THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
SEPTEMBER, 1944

ORIGINAL ARTICLES

STUDIES ON THE MECHANISM OF THE HYPOTENSIVE EFFECT OF SUBSTANCES ELICITING LEUKOCYTOSIS AND FEVER

By R. D. Taylor, M.D.
AND
Irvine H. Page, M.D.
INDIANAPOLIS, IND.

(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital)

Many clinical states that produce fever and leukocytosis are followed by sustained reduction of elevated arterial blood pressure in patients suffering from hypertension. Some of these are major surgical operations (Volini and Flaxman[20]), pneumonia, sterile or infected abscesses, non-shocking burns[19] and "non-specific" protein reactions. It was inevitable that this latter type of reaction should be considered in relationship with the lowering of blood pressure of hypertensive patients and animals that follows injections of kidney extracts, such as were described by Grollman, Williams and Harrison[6] and workers in this laboratory.[11,12,13] In a progress report concerning reduction of blood pressure with kidney extract, Page, Helmer, Kohlstaedt, Kempf, Corcoran and Taylor[14] stated that, "Almost nothing is known concerning the manner in which kidney extract lowers blood pressure," and that, "Pyrogenic and local tissue reaction may contribute to the lowering of blood pressure in some patients but it appears unlikely to be the chief cause." The work of Rodbard and Katz[17] who observed greater reduction of the blood pressure of hypertensive dogs with abscesses following implantation of kidney tissue, than animals with similar lesions produced by implants of other tissue, would seem to substantiate this feeling. More recently Remington, Cortland, Drill and Swingle[16] have demonstrated that reduction of arterial pressure of rats by extracts of kidney occurs without the participation of fever.

On the other hand, several investigators have suggested that these results were due entirely to "non-specific" reactions and have discounted any specific hypotensive qualities of kidney extracts. Thus Chasis, Goldring and Smith[2] found the blood pressure of hypertensive patients decreased during the reaction to intravenous injections of typhoid vaccine. They observed equally great falls in pressure when the rise in temperature was prevented by administering large doses of

XUM

aminopyrine. Schales, Stead and Warren[18] reduced arterial pressure by intramuscular injections of a kidney extract whose proteins were denatured by treatment with sulfuric acid. Prinzmetal, Alles, Margoles, Kagland and Davis[15] obtained similar results with heat-inactivated tyrosinase. All of these workers felt their results were due to "non-specific" protein reactions but, save for the elimination of fever as a cause by Chasis, Goldring and Smith,[2] no attempt was made to determine by what mechanism such reactions might reduce arterial pressure in hypertension. Without raising the question of specific blood pressure reducing qualities of kidney extract, still an explanation of the mechanism of pyrogenic hypotension is needed.

Reactions of this type are usually accompanied by a rise in the W.B.C. count due to granulocytosis. The fact that granulocytes are known to contain large amounts of histamine, a hypotensive agent, as well as proteolytic enzymes, led us to consider the possibility of a relationship between pyrogenic leukocytosis and the effects of pyrogens on arterial blood pressure. The present study was undertaken to ascertain whether or not leukocytosis as such causes a decrease in the elevated arterial pressure of experimental renal hypertension in dogs and malignant hypertension in human beings.

Methods. The dogs were made hypertensive by the silk perinephritis method of Page.[10] Blood pressure was measured daily by direct intra-arterial puncture of the femoral artery. The dogs were not studied further unless the mean pressure on 10 or more successive days was stabilized above 160 mm. Hg.

In one procedure, sterile abscesses were produced by injecting 1.5 to 2.5 cc. of turpentine into the axillary tissue of hypertensive and normal animals. For another, pus from these lesions was then aspirated and injected subcutaneously and intraperitoneally into hypertensive dogs. Each of these animals received 40 to 60 cc. of sterile pus daily. In a third series the leukocyte-producing factor of necrotic tissue described by Menkin, Kodish and Warren[8] was prepared by Dr. O. M. Helmer. Ten to 20 cc. of this material was injected subcutaneously or intravenously into hypertensive animals. The change in W.B.C. counts was followed by counting the leukocytes in heparinized blood drawn from the femoral vein. In a fourth series leukocytosis was produced by injecting 10 to 15 cc. of a 70% solution of acetyl methylamine intramuscularly, as suggested by Zondek and Bromberg.[23]

The patients studied were terminal malignant hypertensives from the Lilly Clinic. The diagnosis of malignant hypertension was made according to the classification of Keith, Wagener and Kernohan,[7] that is, by the demonstration of papilledema and retinal hemorrhages. The terminal state was determined by the presence of clinical uremia, or by the demonstration that renal function, as measured by the diodrast Tm, was not compatible with more than a few weeks' survival (Corcoran, Taylor and Page[4]). Blood pressures were taken as often as indicated by the auscultatory method. White blood counts were made from finger-tip blood.

The substances injected intravenously into these patients was prepared by Dr. A. A. Plentl of this laboratory. In the first series of experiments, the material used was an albumin fraction of pork blood. The serum to be fractionated was so decanted from the R.B.C. that the buffy layer of leukocytes was contained in it. To it was added an equal volume of 3 M $(NH_4)_2SO_4$ and the pH of the mixture brought to 6.5 by addition of 1 N H_2SO_4. The precipitate was removed by filtration and discarded. The concentration of $(NH_4)_2SO_4$ in the filtrate was slowly increased from 1.5 to 2.1 M by the rotating cellophane membrane technique. The precipitated albumin was collected, dissolved in a small volume of water, and fractionally precipitated by succes-

sive adjustments of $(NH_4)_2SO_4$ concentration to 2, 2.15 and 2.4 M in a rotating membrane. The 2.4 M precipitate was separated by filtration, dissolved in distilled water, dialyzed against running tap water for 24 hours, and then against distilled water for 24 hours. The solution was made up to contain 8% protein, and sterilized by Seitz filtration. Thirty to 120 cc. of this solution was given on 18 occasions to 5 patients with malignant hypertension.

In a second series of experiments, human W.B.C. were extracted and injected intravenously into a patient with malignant hypertension. The W.B.C. were collected by suction from the buffy layer of 100 liters of human blood. Complete separation from the R.B.C. was effected by repeated centrifugation. The cells were then suspended in 3 volumes of distilled water. The suspension was stirred vigorously for 45 minutes, allowed to stand in the ice-box overnight, and again stirred for 45 minutes. Enough NaCl was then added to make a 4% solution. The mixture was dialyzed against tap water for 24 hours and filtered. The filtrate was adjusted to 2 M with $(NH_4)_2SO_4$ in a rotating cellophane bag. The precipitate was separated by filtration and dissolved in the least volume of distilled water. The filtrate was adjusted to 4.1 M with $(NH_4)_2SO_4$. This precipitate was collected and dissolved in distilled water.

These two solutions were sterilized with the Seitz filter and injected intravenously in 5 to 15 cc. amounts into a patient with malignant hypertension.

Outline of Methods Testing the Effects of Granulocytes on Hypertension

I. *Hypertensive dogs:*
Leukocytosis induced by:
1. Subcutaneous injection of turpentine with abscess formation.
2. Subcutaneous and intraperitoneal injection of sterile pus.
3. Intramuscular and intravenous injection of Menkin's leukocyte-producing factor.
4. Intramuscular injection of 70% acetyl methylamine.

II. *Patients with malignant hypertension:*
Extracts of leukocytes injected intravenously:
1. Albumin fraction precipitated from pork serum containing buffy layer of cells.
2. Extract of human leukocytes.
   (*a*) Fraction precipitated by 2 M $(NH_4)_2SO_4$.
   (*b*) Fraction precipitated by 4.1 M $(NH_4)_2SO_4$.

Results. Effects of Granulocytes on Hypertension. I. HYPERTENSIVE DOGS. *A.* Leukocytosis induced by:

1. *Subcutaneous Injection of Turpentine With Abscess Formation.* One and a half to 2.5 cc. of turpentine were injected into the axillary tissue of each of 10 hypertensive dogs. The response was much the same in all animals. Within 24 hours the site of injection was indurated, tender and hot; there were 1° to 2° F. of fever, and the blood pressure was 20 to 40 mm. below control levels. On the 2nd day, the lesion was more localized but not fluctuant. The temperature was much the same as the preceding day, but the blood pressure was 10 to 20 mm. lower. By the 3rd day, fluctuation was evident, the temperature was elevated 3° to 4° F., and the blood pressure was at normotensive levels of 110 to 130 mm. Hg. As long as the abscess was encapsulated, the fever and normotension persisted. At the end of 3 to 4 days the lesion began to discharge pus. The temperature returned to normal in 1 to 3 days but the blood pressure took 4 to 5 additional days to reach the previous hypertensive levels. During the first 3 to 4 days the dogs were slightly lethargic and showed evidence of pain;

however, they ate well and moved about normally during the entire experiment. A typical result is illustrated in Figure 1.

2. *Intraperitoneal Injection of Sterile Pus.* Sterile pus from turpentine-induced abscesses was aspirated and promptly injected into 8 hypertensive dogs. Twenty to 60 cc. were given subcutaneously, intraperitoneally, or both, for 6 to 13 days (Table 1). All animals had a rise in temperature of 1° to 3° F. during treatment. One dog developed peritonitis and died, and 1 died of malignant hypertension. These 2 animals had 10 to 40 mm. falls in arterial pressure 2 to 4 days before death, but no other animals showed reduction of blood pressure during or after treatment.

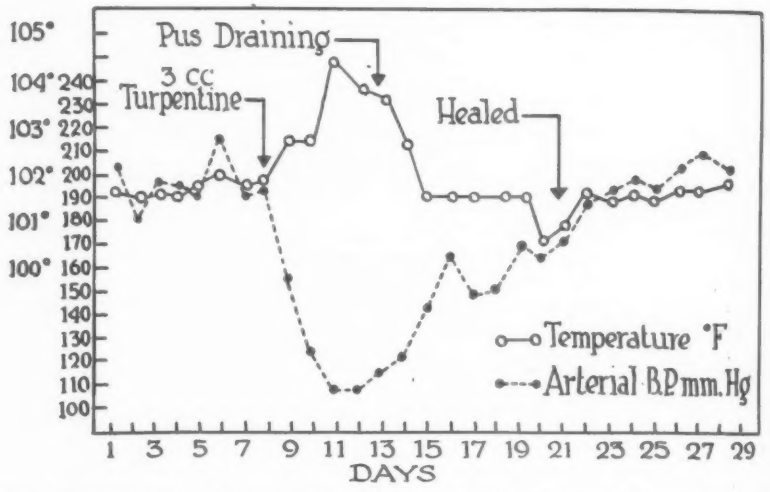


FIG. 1.—Effect of sterile abscesses on blood pressure and temperature of hypertensive dog.

3. *Intramuscular and Intravenous Injection of Menkin's Leukocyte-producing Factor.* Sterile pus was extracted for the leukocyte-producing factor of Menkin. Eight animals received 10 to 15 cc. of this extract intravenously or subcutaneously for 7 to 12 days (Table 2). The average increase of W.B.C. count was 46% (maximum 85% and minimum 28%). No variation of temperature or blood pressure was observed.

4. *Intramuscular Injection of 70% Acetyl Methylamine.* Eight dogs were given daily injections of 10 cc. of a 70% solution of acetyl methylamide for 5 to 13 days (Table 2). The average rise in W.B.C. was 66.4% (maximum 134% and minimum 25%). One dog developed an abscess at the site of injection and experienced a fall in blood pressure similar to those that received turpentine. Another animal was given 20 cc. of the 70% solution on 2 successive days and died of massive hemorrhage from the urinary and respiratory tracts. Autopsy indicated advanced liver necrosis with fatty infiltration. Otherwise there were no untoward results, and neither fever nor hypotensive effects were recorded.

XUM

TABLE 1.—EFFECT ON ARTERIAL BLOOD PRESSURE OF HYPERTENSIVE DOGS RECEIVING INJECTIONS OF STERILE PUS

Dog No.	Amount given (cc. each day)	Route given	Before		Receiving injections			After		
			Av. B.P. (mm. Hg)	Av. body temperature (° F.)	Av. B.P. (mm. Hg)	Av. body temperature (° F.)	Days observed	Av. B.P. (mm. Hg)	Av. body temperature (° F.)	Days observed
1	40	Intraperitoneally	204	101[8]	206	102[6]	7	200	102	10
2	20	Subcutaneously	201	101[6]	202	102[4]	7	207	101[4]	6
3	40	Intraperitoneally	207	101[2]	210	103[8]	10	200	101[2]	6
4	20	Intraperitoneally	199	101[5]	186	104[2]	9	180	101	9
5	40	Subcutaneously	186	102[2]	166	102[6]	13	168	101[8]	10
6	40	Intraperitoneally	197	101	192	101[6]	5	Died of malignant hypertension		
7	50	Intraperitoneally	207	101[6]	213	102[4]	8	196	101[3]	10
8	60	Intraperitoneally	210	101[5]	198	102[3]	8	Died of peritonitis		
Averages	38.7	...	201.4	101[6]	196.6	102[7]	...	191.8	101[5]	

TABLE 2.—LEUKOCYTOSIS INDUCED IN HYPERTENSIVE DOGS BY INTRAMUSCULAR INJECTIONS OF 70% ACETYL METHYLAMINE

	Before				Receiving injections						After			
No.	Days observed	Av. mean B.P. (mm. Hg)	Av. white cells per c.mm. blood	Av. temperature (° F.)	Amount injected daily (cc.)	Days observed	Av. mean B.P. (mm. Hg)	Av. white cells per c.mm. blood	Increase in WBC (%)	Av. temperature (° F.)	Days observed	Av. mean B.P. (mm. Hg)	Av. white cells per c.mm. blood	Av. temperature (° F.)
1	14	190	18,940	101[2]	8	13	180	23,790	26	101	8	184	16,050	101
2	17	185	12,460	101[4]	10	6	176	17,420	40	101[4]	14	188	9,840	101[4]
3	17	181	10,600	102	10	9	182	18,810	77	101[8]	14	191	11,210	101[8]
4	15	204	14,630	101	12	9	198	34,300	134	100[6]	10	194	15,200	100[8]
5	14	197	24,200	100[2]	15	5	182	35,600	46	100	Died from hemorrhage			
6	14	161	12,510	100[4]	10	6	154	26,080	108	100[5]	14	158	12,620	100[4]
7	14	185	13,525	100[7]	12	5	185	20,400	50	101	Died—malignant hypertension			
8	15	160	14,970	100[6]	8	13	140	22,460	50	102[4]	14	158	16,210	100[7]
					Abscess at injection site									
Av.	15	182.8	15,230	100[9]	10.6	8.25	174.6	24,860	66.4	101[1]	12.3	178.8	13,520	101
	LEUKOCYTOSIS INDUCED IN HYPERTENSIVE DOGS BY INTRAMUSCULAR INJECTIONS OF MENKIN'S LEUKOCYTE-PRODUCING FACTOR													
1	14	162	9,780	100[2]	10	7	155	13,740	40	100[6]	10	156	13,460	100[5]
2	14	161	16,000	101[4]	12	7	165	23,385	46	101[6]	10	164	13,820	101[5]
3	10	162	16,700	101[2]	15	6	166	21,300	28	101[2]	10	171	12,100	101
4	14	165	12,540	101[6]	15	8	165	17,830	42	101[4]	14	160	11,315	101[4]
5	14	160	15,525	101[5]	12	9	160	21,480	40	101[6]	14	165	11,420	101[4]
6	14	165	12,510	101[3]	15	12	172	19,560	56	101[6]	14	174	12,370	101[4]
7	11	243	36,060	101[4]	15	9	221	47,190	31	102[2]	Died—malignant hypertension			
8	12	182	21,920	102	20	8	184	40,500	85	101[8]	12	185	19,650	101[8]
Av.	12.8	175	17,630	101[3]	14.25	8.25	173.5	25,620	46	101[5]	12	167.8	13,450	101[3]

XUM

TABLE 3.—EFFECT OF EXTRACT OF PORK SERUM CONTAINING BUFFY COAT ON ARTERIAL BLOOD PRESSURE OF MALIGNANT HYPERTENSIVES

Patient	Amount given (cc.)	Route of administration	Reduction of B.P. 1 to 4+	Duration of reduced B.P.	Type of reduction		Evidence of allergy 1 to 4+	Post-treatment temperature (° F.)	WBC per c.mm. blood	
					Immediate	Delayed			Before treatment	After treatment
1	50	Intravenous	++++	40 min.	+	..	++	98[6]	6,520	15,200
2nd day	100	Subcutaneous	...	...	...	...	...	98[6]	10,800	14,800
3rd day	50	Intravenous	++++	12 min.	+	...	+++	102[2]	6,750	16,750
2	50	Intravenous	++	25 min.	+	...	+++	98[6]	7,850	14,800
3	50	Intravenous	++++	20 min.	+	...	+	102[8]	10,600	25,200
2nd day	50	Intravenous	+++	7 min.	+	...	+	101[8]		
3rd day	80	Subcutaneous	...	...	...	...	...	102[8]	25,800	22,650
4	60	Intravenous	++++	12 hrs.	...	+	++	101	8,700	18,600
2nd day	30	Intravenous	...	...	...	...	+	101	18,600	19,200
3rd day	30	Intravenous	...	...	...	...	...	99	18,400	23,600
4th day	30	Intravenous	...	...	...	...	...	99[2]	23,600	26,200
5	80	Intravenous	++	12 hrs.	...	+	++	Pretreatment aminopyrine	9,200	29,000
2nd day	16	Intravenous	...	...	...	...	+++	98[6]	29,000	25,000
3rd day	30	Intravenous	...	...	...	...	++	99[4]	25,000	12,800
4th day	28	Intravenous	++	12 hrs.	...	+	++++	99[2]	12,800	10,600

EFFECT OF EXTRACTS OF HUMAN WHITE CELLS ON ARTERIAL BLOOD PRESSURE OF PATIENTS WITH MALIGNANT HYPERTENSION

				Extract No. I						
1	18	Intravenous	++++	12 hrs.	...	+	++++	98[6]	6,250	19,700
2nd day	10	Intravenous	...	...	...	...	+++	100	19,700	26,800
				Extract No. II						
2	5	Intravenous	...	...	...	...	++++	102	9,500	42,500

II. Patients With Malignant Hypertension. *A.* Extracts of leukocytes injected intravenously:

1. *Albumin Fraction Precipitated From Pork Serum Containing Buffy Layer of Cells.* An 8% solution of this material was given intravenously on 15 occasions to 5 patients with malignant hypertension. In 3, arterial pressure fell rapidly and remained low for intervals of 25 to 40 minutes. Repetition of the injection 24 hours later produced less marked and less sustained falls in pressure. Each injection was accompanied by evidence of allergic reaction, such as hives, nausea, involuntary defecation and fever. Twenty-four hours after treatment all cases showed leukocytosis, but blood pressure continued at the usual hypertensive levels (Table 3).

On 3 occasions, in 2 patients, the fall in arterial pressure was delayed, occurring 6 to 10 hours after the injection and lasting about 2 hours. However, each was accompanied by evidences of sensitization and could not be reproduced by subsequent injections. These 2 patients maintained pretreatment hypertensive levels in the face of 200% increases of leukocyte count on the days following the treatment (Table 3).

Subcutaneous injections of the material caused no changes in arterial blood pressure.

2. *Extracts of Human Leukocytes.* (*a*) Fraction precipitated by 2 M $(NH_4)_2SO_4$: The injection of this fraction resulted in flushing, pain in the back, chest and joints; and blood pressure fell 100 mm. Hg systolic and 80 mm. diastolic 2 hours after, returning to previous levels within 12 hours, at which time there was a 200% increase in white cell count.

The fall in blood pressure could not be duplicated in this patient 24 hours later, but the evidences of allergic sensitivity were again manifest and the W.B.C. rose to 400% of its normal level.

(*b*) Fraction precipitated by 4.1 M $(NH_4)_2SO_4$: Injection of the second fraction of the washed human leukocytes on 1 patient resulted in hives, perspiration, fever and a 42,500 W.B.C., but without accompanying change in arterial blood pressure.

Discussion. This report is a part of an investigation undertaken to determine the mechanism whereby "non-specific" and inflammatory reactions cause reduction of arterial blood pressure in hypertensive patients and animals. The majority of such reactions are accompanied by fever and leukocytosis, both of which must be considered as having possible relationship to this change in arterial pressure; the former because it is associated with vasodilation and might thus evoke hypotension, and the latter because of the high content of histamine and proteolytic enzymes present in granulocytes. Chasis, Goldring and Smith[2] eliminated hyperpyrexia as the vasodilator responsible for the reduction of blood pressure in "non-specific" reactions. They blocked the temperature rise of hypertensive patients who received reaction-producing doses of typhoid vaccine intravenously by administering large doses of amidopyrine before the injection of

vaccine, and observed equally marked vasodilation, renal hyperemia and reduction in blood pressure as in febrile patients.

Our studies have eliminated leukocytosis as well as large collections of leukocytes as components in the mechanism that causes vasodilation and lowered blood pressure. Neither injections of sterile pus nor the peripheral leukocytosis that followed injection of Menkin's leukocyte-producing factor and 70% acetyl methylamine had an effect on the mean arterial pressure of hypertensive dogs. Likewise, leukocytosis and extracts of W.B.C. did not consistently lower the blood pressure of patients with malignant hypertension. The lowered pressures that were observed were clearly due to allergic reactions. In light of these findings, it seems safe to assume that neither fever nor granulocytes cause the vasodilation that occurs in inflammation and "non-specific" reactions.

This evidence, in conjunction with the observation that fresh, sterile pus which should contain any hypotensive material that might result from denaturation of tissue proteins by inflammation or proteolytic enzymes, failed to reduce blood pressure; and would seem to point to some alteration in febrile states of the homeostatic mechanism responsible for maintenance of vascular tone and elevated blood pressure. By this we mean that some humoral agent akin to those that induce leukocytosis, cellular diapedesis and fever itself, in inflammation (Menkin, Kodish and Warren[8]) may be selectively antagonistic or depressant to a body function that has to do with the maintenance of blood pressure.

Such a function could be ascribed to the adrenal cortex, inasmuch as Goldblatt,[5] Page,[9] Collins and Wood,[3] and Blalock and Levy[1] have all demonstrated that renal hypertension is difficult to induce or sustain in adrenalectomized animals treated with salt and adrenal cortical extracts. More recently, Weil and Browne[21,22] have demonstrated a qualitative change in adrenal cortical function as the result of systemic injury (operation, fracture, burn, febrile illness). This change is reflected in increased urinary excretion of cortin-like material with diminished excretion of 17-ketosteroids and the establishment of negative nitrogen balance. Such insults to the body economy could also depress the secretion of another adrenal factor which maintains vascular reactivity in hypertension and thus account for the decreased arterial pressure which often follows it. As other explanations of this type of hypotension fail, some such concept comes to deserve further study.

Summary and Conclusions. 1. The mechanism of reduction of arterial blood pressure of hypertensive patients following "non-specific" or inflammatory reactions is unexplained.

2. Fever has been eliminated as the etiologic agent.

3. The present studies have ruled out the second most common component of such reactions, leukocytosis, as the hypotensive agent.

4. Neither injection of sterile pus nor peripheral leukocytosis resulting from injection of Menkin's leukocyte-producing factor and 70% acetyl methylamine affects the blood pressure of hypertensive dogs.

5. It is suggested that "non-specific" and inflammatory reactions impair that function of the adrenal cortex that has to do with the maintenance of vascular reactivity and elevated blood pressures so eliciting reduction of arterial pressure.

Lucile V. Clary, R.N., contributed materially to this study.

REFERENCES

1. Blalock, A., and Levy, S. E.: Ann. Surg., **106**, 826, 1937.
2. Chasis, H., Goldring, W., and Smith, H. W., Jr.: J. Clin. Invest., **21**, 369, 1942.
3. Collins, D. A., and Wood, E. H.: Am. J. Physiol., **123**, 224, 1938.
4. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Proc. Centr. Soc. Clin. Invest., **16**, 52, 1943.
5. Goldblatt, H.: J. Am. Med. Assn., **108**, 675, 1937.
6. Grollman, A., Williams, J. R., Jr., and Harrison, T. R.: J. Biol. Chem., **134**, 115, 1940.
7. Keith, N. M., Wagener, H. P., and Kernohan, J. W.: Arch. Int. Med., **41**, 141, 1928.
8. Menkin, V., Kodish, M. A., and Warren, A. A.: Am. J. Med. Sci., **205**, 363, 1943.
9. Page, I. H.: Am. J. Physiol., **122**, 352, 1938.
10. Page, I. H.: Science, **89**, 273, 1939.
11. Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Fouts, P. J., Kempf, G. F., and Corcoran, A. C.: Proc. Soc. Exp. Biol. and Med., **43**, 722, 1940.
12. Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Fouts, P. J., and Kempf, G. F.: J. Exp. Med., **73**, 7, 1941.
13. Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Kempf, G. F., Gambill, W. D., and Taylor, R. D.: Ann. Int. Med., **15**, 347, 1941.
14. Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Kempf, G. F., Corcoran, A. C., and Taylor, R. D.: Ann. Int. Med., **18**, 29, 1943.
15. Prinzmetal, M., Alles, G. A., Margoles, C., Kagland, S., and Davis, D. S.: Proc. Soc. Exp. Biol. and Med., **50**, 288, 1942.
16. Remington, J. W., Cortland, G. F., Drill, V. A., and Swingle, W. W.: Am. J. Physiol., **140**, 627, 1944.
17. Rodbard, S., and Katz, L. N.: Am. Heart J., **26**, 114, 1943.
18. Schales, O., Stead, E. A., Jr., and Warren, J. V.: Am. J. Med. Sci., **204**, 797, 1942.
19. Taylor, R. D., and Page, I. H.: Unpublished observations.
20. Volini, L. F., and Flaxman, N.: J. Am. Med. Assn., **112**, 2126, 1939.
21. Weil, P. G., and Browne, J. S. L.: Science, **90**, 445, 1939.
22. Weil, P. G., and Browne, J. S. L.: J. Clin. Invest., **19**, 772, 1940.
23. Zondek, B., and Bromberg, Y. M.: Am. J. Med. Sci., **205**, 82, 1943.

FURTHER STUDIES ON THE LEUKOCYTOSIS-PROMOTING FACTOR AND ON NECROSIN IN INFLAMMATORY EXUDATES*

By Valy Menkin, M.D.

ASSOCIATE IN RESEARCH AND FELLOW OF THE JOHN SIMON GUGGENHEIM MEMORIAL FOUNDATION, FREE HOSPITAL FOR WOMEN, BROOKLINE, MASS.

(From the Fearing Research Laboratory)

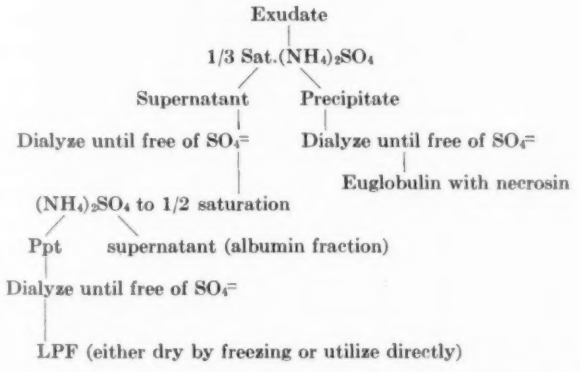
Inflammation is the basic response to infectious processes.[1] As such, an important factor in its pathogenesis is a development of severe cellular injury. The inflammatory reaction is initiated by a

* This is Paper 30 of a series entitled "Studies on Inflammation." These studies were aided by grants from the Johnson and Johnson Research Foundation and from the Dazian Foundation for Medical Research. Read in part before the Boston Society of Biologists, March 15, 1944.

disturbance in fluid exchange. It then proceeds through an orderly and fundamental pattern. The steps are in many of the sequences referable to the liberation of biochemical units liberated in turn by injured cells. Damaged cells may be regarded as having a totally different chemistry as a result of their deranged cellular metabolism. In this connection, several years ago it has been found that the mechanism of increased capillary permeability and of leukocytic migration is referable to the liberation of a crystalline nitrogenous substance recovered from exudates and termed leukotaxine.[2] Leukotaxine is concerned only with local migration or diapedesis of polymorphonuclear leukocytes.[3] As such it fails to alter the number of circulating leukocytes when introduced into the circulation.

Leukocyte-promoting Factor. Nevertheless there seems to exist a leukocytosis-promoting factor in exudates capable of explaining the systemic leukocytosis frequently accompanying inflammatory processes, for when the exudative material is introduced into the circulating blood stream of a dog, this is followed by a rise in the number of circulating leukocytes.[4] No such prompt response can be obtained with blood serum, bacteria, or saline. This factor is thermolabile and non-diffusible. These facts have suggested its protein nature. Indeed, fractionation with ammonium sulfate indicate that the activity is concentrated in the pseudoglobulin fraction of exudates.[5] The present adopted scheme has been somewhat simplified:

SCHEME OF EXTRACTING THE LEUKOCYTOSIS-PROMOTING FACTOR (LPF) AND NECROSIN FROM EXUDATES



The effect of an injection of the LPF, as we term the leukocytosis-promoting factor, is on the bone marrow, inducing a discharge of immature or non-filamentous forms of granulocytes into the circulation.[4] I shall presently return to the question of the effect of the leukocytosis-promoting factor on the bone marrow.

The LPF is absent in normal blood serum, but it is present in the sera of animals with concomitant inflammation.[6] Such observations and others seem to indicate that the material reaches the bone marrow by penetrating from the site of acute inflammation into the circulating blood.

The active principle is obtained readily from the exudate of man.[7] In the first series of experiments an average increase of over 100% in the number of circulating leukocytes was demonstrated by an injection of human LPF. At present we can obtain even greater potency.[8] These results suggest possible clinical application. The rise is essentially due to an outpouring of granulocytes. This is accompanied by an abundance of immature forms.

Recently the effect of this active biologic substance on the bone marrow has been studied.[8] In Figure 1 the appearance of the femoral bone marrow is seen following an injection of the pseudoglobulin fraction of normal blood serum. As you note, the bone marrow appears relatively normal. Contrast this effect when only 13.5 mg. of potent LPF is injected intravenously. Two days afterwards the animal is sacrificed. Note the active growth or hyperplastic response on the part of the bone marrow (Fig. 2). This proliferative response involves primarily the granulocytic forms and the megakarocytes.

One may conclude, then, that the existence of a leukocytosis-promoting factor in exudates offers a reasonable explanation for the mechanism of leukocytosis accompanying numerous inflammatory processes. As the prognosis of some infectious conditions has been referred to some some extent to the number of circulating leukocytes,[13] the obvious clinical implication of the LPF in reinforcing other chemotherapeutic agents deserves exploration. Finally, the prompt growth response of this material on the bone marrow may also prove to have, besides theoretical interest, clinical possibilities in various sluggish conditions of the bone marrow.

Necrosin. I now turn to another more recently identified chemicobiologic unit from inflammatory exudates. Neither leukotaxine nor the LPF induces any appreciable degree of tissue injury. Yet an inflammation is a manifestation on the part of the host of severe cellular damage. When whole exudative material is injected locally into a rabbit, a marked and appreciable response can be elicited. A search for the factor responsible for injury was undertaken. Without burdening you with too much detail, it has been found that either the euglobulin fraction or associated with that fraction of exudates, there seems to exist a factor capable of reproducing the acute injurious edematous response of inflammation.[9] Material introduced into such an area fails to disseminate to the tributary lymphatic nodes. This is referable primarily to a lymphatic blockade, which in itself is a sign of marked local injury. Besides causing damage to the draining lymphatics, the euglobulin fraction of exudate likewise induces injury to the vascular channels in the form of small thrombi. If the factor causing injury and recovered from inflammatory exudate is a euglobulin, then it may perhaps be an atypical euglobulin; for it fails to be dissolved in the presence of electrolytes. The effect is scarcely referable to denaturation during dialysis of the $SO_4^=$ for an inactive fraction is obtained by similarly fractionating blood serum with $(NH_4)_2SO_4$ at one-third saturation, or sometimes by merely dialyzing whole exudative material and recovering the precipitate. Furthermore, the reason

XUM

for this statement lies in the fact that the whole exudate is injurious *per se*, inducing likewise a lymphatic blockade. No other fraction so far studied except the euglobulin fraction of exudates is capable of

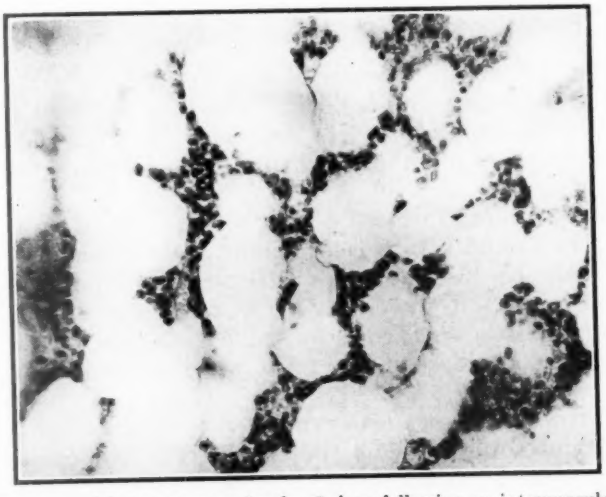


FIG. 1.—The femoral bone marrow of a dog 2 days following an intravascular injection of 14.5 mg. of pseudoglobulin derived from normal blood serum.

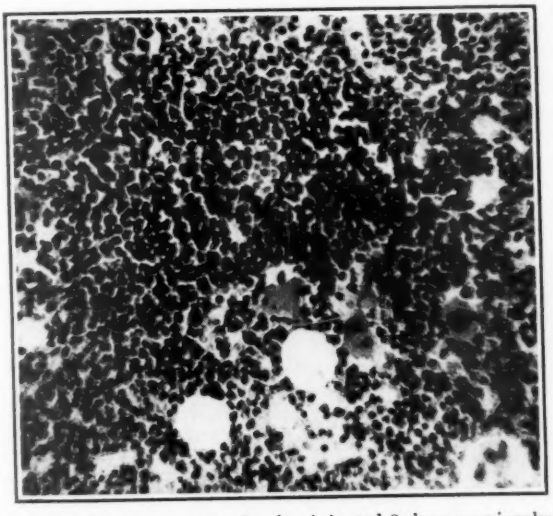


FIG. 2.—The femoral bone marrow of a dog injected 2 days previously with 13.5 mg. of leukocytosis-promoting factor. The hyperplastic response is striking. The proliferative effect involves primarily granulocytic elements and also megakaryocytes.

reproducing the acute injurious response seen in inflammation. In brief, if there is any denaturation, then that seems to be a natural phenomenon occuring *in vivo* and caused by the injured cell at the site of inflammation. For the sake of convenience this fraction of exudates

has been termed "necrosin." Its presence offers a reasonable explanation for the pattern of injury in inflammation. Now, if precisely the same procedure is repeated with non-hemolyzed blood serum, as stated above, the injected euglobulin fraction fails to display an acute inflammatory reaction with superficial necrosis, and the lymphatics remain unoccluded.

The first morphologic evidence of injury as elicited by necrosin is a swelling of the collagenous bundles. This may be found 10 minutes after intracutaneous injection of necrosin. No such effect appears upon the introduction of the euglobulin fraction obtained from normal blood serum.

Necrosin is absent in blood serum, but it is found present in the serum of an animal with a concomitant acute inflammation. Such evidence indicates that the active principle probably penetrates from the site of injury into the circulating blood stream. These observations suggest that a so-called focus of infection may indeed have far-reaching effects by liberating necrosin, which in turn penetrates into the circulation.

For this reason, observations were recorded on the effect of necrosin when introduced directly into the circulation. The animal may at first be prostrated. It may have symptoms of diarrhea and of vomiting; and, in general, the dog presents a very apathetic and listless appearance. There may be hemorrhage throughout the length of the gastro-intestinal tract. A hydrothorax involving both cavities has been encountered; but in general the constant features are injury to the liver and, very frequently, to the kidneys. The liver may show patchy areas of fatty necrosis which, on microscopic section, appear as heterogenous zones of fat deposits interspersed among foci of leukocytic infiltration. The picture is not unlike that seen in hepatic focal necrosis. Sometimes one encounters areas of severe cellular damage in which the cell contents are replaced by a fine stippling which does not take the iron stain. The effect on the kidney is rather striking. The lumina of the tubules may show a lining with swollen, vacuolated cells having irregular contours. Interspersed are seen foci of leukocytic infiltration. The picture is not dissimilar to and, in fact, is reminiscent of a pyelonephritis.[9]

Necrosin fails to lower the blood pressure of a cat in contrast to histamine. This, however, does not necessarily mean that necrosin may not play an important rôle in traumatic shock as one of the actively participating components of the phenomenon.[10]

There are two other phenomena elicited by necrosin which I should like to discuss before terminating the present paper. In the first place, the injection of necrosin in contrast to the LPF induces a leukopenia.[10] The blood count may fall to a level of 1000 or 2000 per c.mm. Only later the leukopenia may be replaced by a leukocytosis. This leukocytosis may well be a secondary phenomenon referable to the liberation of the LPF by organs injured in turn by necrosin. This observation may prove of real significance, for necrosin is the only fraction recovered from exudates which has been found capable of

inducing such a sharp fall in the number of circulating leukocytes. It is to be recalled, for instance, in this connection, that the pathologic picture of local vascular thrombi and leukopenia encountered in typhoid fever is reminiscent of the effects produced by the injection of necrosin. One wonders whether a number of clinical conditions with leukopenia may not be referable to the liberation of an abundant amount of necrosin at the site of inflammation. The finding that necrosin induces leukopenia has been utilized in the further purification of the LPF from exudates. Recent observations to be subsequently reported *in extenso* by Major A. Mirsky and the writer, indicate that the injury factor in necrosin contains proteolytic activity which can be at least partially neutralized by an antiprotease. These facts suggest that plerosin is a proteolytic enzyme or that it is at least associated in its present state of purification with such an enzyme. On the other hand, the pyrogenic factor in the euglobulin fraction of exudate is definitely non-proteolytic in activity.

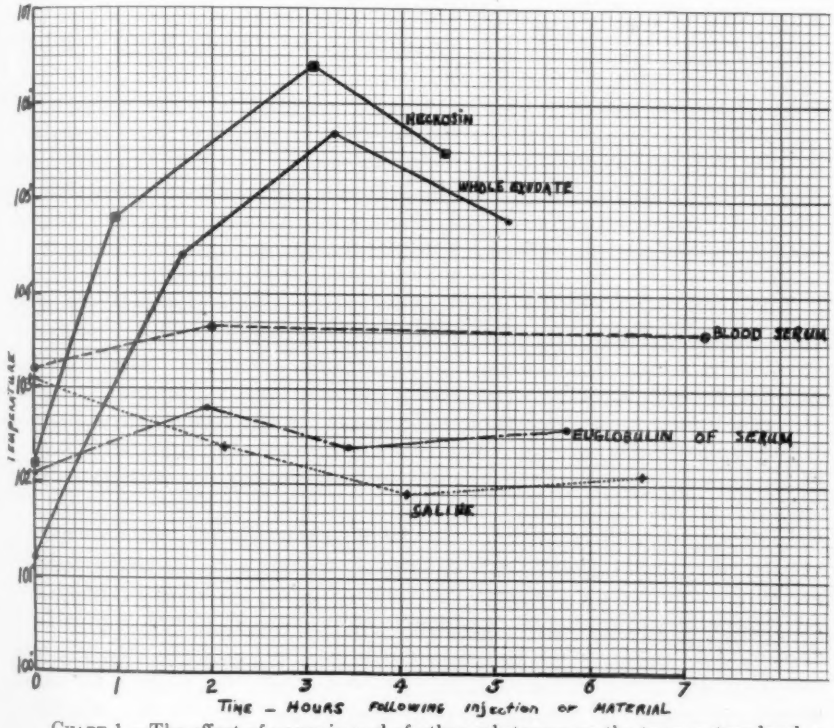


CHART 1.—The effect of necrosin and of other substances on the temperature level of the rabbit.

Finally, I should like to dwell on the effect induced by necrosin on temperature.[9,10] Necrosin injected into a dog induces fever. The LPF or other protein fractions procured from exudates fail to do so.[10] The elevation in temperature may be very marked: 3° to 5° F. Of late it has been found that the rabbit is extremely susceptible to the

effect of necrosin as regards temperature levels (Chart 1). Note that the whole exudate (or the dried exudate) induces fever. Necrosin reproduces the same effect. Hemolyzed serum does the same, whereas non-hemolyzed serum fails to do so to any appreciable effect. The significance of this finding may prove of value in determining the immediate factor involved in the onset of fever in malaria. It is conceivable that the release of the contents of red corpuscles into the circulation may likewise liberate an abundance of necrosin which in turn would be responsible for the pyrogenic effect. The evidences which are now being obtained indicate that the rabbit may prove to be a very suitable test animal for the determination of necrosin in various body fluids. Studies are now under way to determine the factor in necrosin which is responsible for the production of fever. This latter seems to be referable to a highly heat-stable component in contrast to the labile injury factor in necrosin. Studies are also in progress in an endeavor to determine if this substance acts by stimulation of the heat centers. In brief, sufficient material has been advanced in the present discussion to indicate that necrosin liberated at the site of injury in turn by penetrating into the circulating blood stream may well be responsible for the primary mechanism of fever production accompanying inflammatory processes.

Conclusion. Injured cells as encountered in inflammation display a wholly different chemistry than normal cells. By releasing various common denominators such as leukotaxine, the LPF, necrosin, glucose,[12] even possibly urea,[12] the cell in turn initially injured by any sort of irritant, be it viable or non-viable, reasonably accounts by an altered chemistry for the stereotyped reaction of inflammation.

Further studies on the purification of the leukocytosis-promoting factor from inflammatory exudates yield by a somewhat simplified procedure, a potent biologic fraction. The substance affects both cellular growth response in the bone marrow and the number of circulating leukocytes. A leukocytosis ensues in the blood stream, and a hyperplastic response on the part of granulocytes and megakaryocytes is encountered in the bone marrow following the intravascular injection of this substance.

Necrosin, associated with the euglobulin fraction, of exudates may consist of several distinct components. Two of these are particularly striking. One is concerned with cellular injury, having proteolytic enzymatic activity, while another is pyrogenic in effect. Further studies are being conducted to determine the nature of these two components. The rabbit is found to be a good test animal for the determination of necrosin in various body fluids by its susceptibility in developing fever. The studies strongly suggest that the primary mechanism of fever associated with inflammatory processes may be referable to the absorption into the circulation of the pyrogenic component of necrosin.

REFERENCES

1. MENKIN, V.: Dynamics of Inflammation, New York, Macmillan, 1940.
2. MENKIN, V.: J. Exp. Med., **67**, 129, 1938.
3. MENKIN, V.: J. Exp. Med., **67**, 145, 1938.

XUM

4. MENKIN, V.: Am. J. Path., **16**, 13, 1940.
5. MENKIN, V.: Arch. Path., **30**, 363, 1940.
6. MENKIN, V., and KADISH, M. A.: Arch. Path., **33**, 193, 1942.
7. MENKIN, V., KADISH, M. A., and SOMMERS, S. C.: Arch. Path., **33**, 188, 1942.
8. MENKIN, V.: Am. J. Path., **19**, 1021, 1943.
9. MENKIN, V.: Arch. Path., **36**, 269, 1943.
10. MENKIN, V.: Proc. Soc. Exp. Biol. and Med., **54**, 184, 1943.
11. MENKIN, V.: Am. J. Physiol., **134**, 517, 1941.
12. MENKIN, V.: Am. J. Physiol., **138**, 396, 1943.
13. ROBERTSON, D. H., and FOX, J. P.: J. Exp. Med., **69**, 229, 1939.

STUDIES ON PALMAR SWEATING*†

BY CAPT. JACOB J. SILVERMAN, M.C., A.U.S.
AND
LIEUT. COL. VERNON E. POWELL, M.C., A.U.S.
(From the Kennedy General Hospital, Memphis, Tenn.)

PART I. A TECHNIQUE FOR THE STUDY OF PALMAR SWEATING

STUDIES dealing with the sweat mechanism are usually handicapped by complicated techniques. A complete review of the many methods to measure sweat is given by Kuno.[15] Depending upon the amount and type of perspiration to be studied the following techniques have been used in the past: (1) Respiratory chamber; (2) balances for the measurement of body weight; (3) measurement of the whole body surface, such as enclosing the body in a rubber bag; (4) measurement of one limb or a small area of the skin by enclosing the part and introducing dry air current and collecting the moisture; (5) direct observation of sweat drops by means of a skin microscope; (6) capillary tube method by inserting a capillary tube directly into a sweat duct; (7) testing for chlorides; (8) collecting the sweat directly such as with a blotting paper; (9) utilizing a galvanometer hook-up and studying the galvanic skin reaction; (10) colorimetric methods.

Colorimetric methods are most widely used in clinical medicine today, and the most popular one is the technique devised by Minor.[16] This method depends upon the color reaction produced by the interaction of iodine and starch in the presence of moisture. Guttmann[9] used chinazarin as a base and obtained more satisfactory results. In the presence of sweat, a dark stain is produced and, depending upon the extent and intensity, the degree of sweating may be graded. Roth[18] applied cobalt directly to the part to be tested, and in the presence of sweat the blue color faded. These methods, however, are not always reliable, since the color reaction may be modified by the humidity. Another disadvantage is that, unless photographs are taken, the records obtained lack permanency.

To overcome these objections a colorimetric technique for measuring

* Brigadier General Royal Reynolds, Kennedy General Hospital, encouraged the writing of this paper. Lieut. Morris Kaslow gave technical assistance.
† No objection to publication, Bureau of Public Relations, War Department, Washington, D. C.

palmar sweating[20] of the palm and finger tips has been devised. This method has the following advantages:

1. *Availability.* The materials to be used are not critical and can be obtained at any modern pharmacy. The only chemicals used are alcohol, tannic acid or potassium ferrocyanide, and ferric chloride.

2. *Economy.* Over 1000 tests can be done at less than $.75.

3. *Objectivity.* Over 4000 tests have been graded by different observers and there is remarkable agreement in the classification. The test is a qualitative and quantitative measure of sweat.

4. *Practicability.* The test requires no elaborate equipment, leaves practically no stain, is easy to perform and with experience more than 25 examinations can be done in 1 hour.

5. *Permanency.* The records obtained are stable, not affected by humidity and can be used as part of a clinical record such as a roentgenogram or an electrocardiogram.

Method. The method now described depends upon the interaction of a chemically treated paper with sweat containing a reacting salt.

(*a*) *Preparation of Paper.* A 5% solution of tannic acid is prepared in distilled water, filtered and poured in a flat-bottom glass dish. Ordinary mimeograph paper is used and is allowed to soak in this solution for approximately 3 minutes. Metal containers are avoided. The paper is then dried and cut to desired dimensions. Where tannic acid is not available, a 5% solution of potassium ferrocyanide is used. The latter solution has the disadvantage of being less stable.

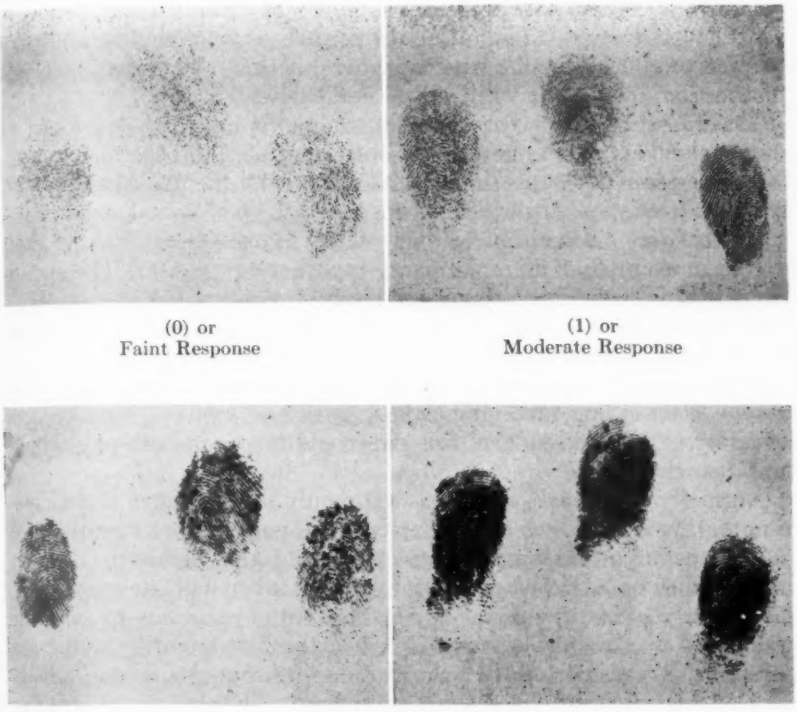
(*b*) *Preparation of the Salt.* Ordinary U.S.P. tincture of ferric chloride is diluted 1 part with 3 parts of alcohol, thus making a 25% solution. This preparation is stored in a well-stoppered, light-proof bottle.

(*c*) *Technique of Application.* The part to be tested is first thoroughly dried with an ordinary hair blower or an electric fan. A liberal amount of the prepared solution of ferric chloride is then evenly applied to the area with an ordinary cotton-tipped wooden applicator. The area is then dried thoroughly, and immediately thereafter contact is made between the chemically treated paper and the part to be tested. Contact is maintained for exactly 3 minutes. The procedure is explained to the patient before the test and it is advisable to have the patient in a comfortable position. For the study of palmar sweating the patient is seated beside a table with the forearm resting completely and evenly on its top.

(*d*) *Chemical Reaction.* The arrangement of the active sweat glands is portrayed upon the chemically treated paper. Sweat is approximately 99% water, and will carry with it in solution the readily soluble ferric chloride. The size and intensity of the pattern is directly proportional to the amount of sweat excreted. In the tannic acid technique the tannic acid reacts with iron to form a stain on the paper ranging between grey-blue and blue-black. The combination of tannic acid and iron salts is used commercially in the preparation of writing inks. When potassium ferrocyanide is used, the interaction with ferric chloride leaves a blue stain. This is the familiar Prussian blue reaction.

(*e*) *Interpretation of Results.* Using the tannic acid technique, the prints obtained on the paper fall into 4 categories: (0) or faint response; (1) or moderate response; (2) or strong response; and (3) or intense response. A (0) or faint response is characterized by fine, pin-point scattered dots, faintly grey in color. A (1) or moderate response is characterized by thicker dots and darker in shade. These dots are more numerous and begin to take on a linear pattern. A (2) or strong response is characterized by black speckles arranged in different sizes and occasionally appear confluent. A (3) or intense response shows diffuse blackening with thick blotches. In the potassium ferrocyanide

technique the results are analogous except that the end-points are blue. Examples of the prints using the tannic acid technique are shown (Fig. 1).



(0) or Faint Response

(1) or Moderate Response

(2) or Strong Response

(3) or Intense Response

FIG. 1.—Classification of the sweat response as seen in the palmar aspect of the fingers.

PART II. THE SIGNIFICANCE OF PALMAR SWEATING

Sweating of the body occurs under diverse conditions. Its thermoregulatory function is well known. That temperature control of the body is not the sole function of sweating has now been well established. For the purpose of classification, sweating may be conveniently divided into the following headings, recognizing that they include mechanisms, localities and etiologic concepts.

1. *Thermo-regulatory.* This type is most important in that it controls body temperature. It is partly because of this function that man is able to inhabit the various zones of the world. It has been shown[15] that in this type of sweating the sweat glands over the entire body surface except those of the palms and soles take part.

2. *Excretory.* Qualitatively sweat is similar to urine but only under unusual pathologic conditions, such as in uremia, will any significant urinary component be excreted. During exercise, however, there is an increase of lactic acid in sweat. Sweat contains approximately 99% water and is, therefore, the most dilute of animal fluids. Its most

important solid constituent is sodium chloride, and during excessive sweating hypochloremia may result. Water-soluble vitamins are also found in sweat.

3. *Drugs.* Coal tar products produce sweating; their action is central. Autonomic stimulating drugs such as acetycholine and pilocarpine produce sweating by a peripheral action. The pharmacologic mechanism in sweating will be discussed below.

4. *Axillary.* The sweat glands in the axilla are fully developed at puberty and actively secrete under both emotional and thermal stimuli. According to Kuno[15] the discharge of sweat from the axilla carries with it a characteristic scent which is considered to be of sexual significance.

5. *Gustatory.* Ingestion of spicy foods evokes sweat on the face, and is an example of a cranial parasympathetic response. The significance of this type of sweating is not clear.

6. *Spinal Reflex.* This type of sweating occurs in the transverse syndrome of the spinal cord, and is seen only in pathologic conditions.

7. *Emotional.* Emotional, intellectual and sensory stimuli will cause a type of sweating involving palms, soles and axillæ. This type of sweating is the main topic of this paper and is seen in both physiologic and disturbed states.

Normally emotional sweating is commonly seen in states of anticipation and has sometimes been referred to as anticipatory sweating. A student before an examination, an expectant father before the delivery of his child, or a draftee waiting for his number will show sweating, particularly of the palms. The relationship of emotions to sweating was noted by Sanctorius[19] in 1614, when the first scientific studies on perspiration were performed. Sanctorius shrewdly observed: "a body which is at rest whilst the mind is violently agitated has a stronger perspiration and less weight than a body that is strongly moved whilst the mind is at rest." Interestingly, Hermann and Luchsinger[10] in 1878 referred to the profuse sweating of the foot pads of cats as "Angstschweiss." The relationship of palmar sweating to emotional stress or strain has expression in many fields of human endeavor. A baseball player will moisten the palm of his glove or hand with saliva in anticipation of a play. A woodman performs a similar act when he is about to grip his axe. As Kuno[15] points out, moistening the palms is a physiologic property and does not have an ethnologic distribution. The expression "spitting on the palm" is found in many languages, and in the Chinese and Japanese languages the expression conveys a meaning of physical and mental stress.

The relationship of sweating to mental and emotional stimuli indicates a cortical control. Bechterew[1] in 1905 demonstrated that stimulation of a localized area of the cortex evoked sweating. Bieber and Fulton[2] indicated that this area (area 6 of Brodman) was also important in the grasp reflex. Kennard, Viets and Fulton[13] showed on clinical grounds that pathologic lesions in this area produced impairment of skilled movements, forced grasping, vasomotor changes and sweating. Rabiner[17] found that patients with so-called autonomic imbalance without any demonstrable organic disorder showed reflex grasping

XUM

when in a state of panic. That the cortex is not the only pathway in sweating is suggested by the work of Wang, Pan and Lu.[22] These investigators demonstrated that following section of the brain above the level of the hypothalamus, a sweat response could be obtained by faradic stimulation of afferent nerves. The relationship between sweating and parasympathetic centers in the diencephalon was noted by Cushing,[4] who observed profuse sweats, vomiting and vasomotor changes after injections of pilocarpine and pituitrin in the region of the interbrain. Cushing looked upon the interbrain as a "station for vegetative impulses easily affected by psychic impulses," and suggested that conditions might conceivably arise whereby hormones discharged in sufficient strength would call forth a parasympathetic response.

On anatomic grounds it has been established that the sweat fibers originate from the cells of the lateral horn of the spinal column and travel along the sympathetic trunk. Extirpation of the sympathetic fibers supplying the lower extremity causes anhydrosis of most of the lower extremity. These sweat fibers along with the other sympathetic components are contained in the peripheral nerves. Stimulation of the sciatic nerve of the cat, for example, will produce sweating of the foot pads. Severing a peripheral nerve will leave its innervated part anhydrotic.

Although sweating on anatomic grounds travels along a sympathetic pathway, pharmacologically it behaves as a parasympathetic mechanism. Pilocarpine, physostigmine, and acetylcholine will stimulate sweating; atropine will inhibit it. Epinephrine, a powerful sympathetic stimulator, does not cause sweating in man. Ergotoxin, which is a sympathetic inhibitor, has practically no affect on sweating. Dale and Feldberg[6] showed that a sympathetic nerve may carry postganglionic fibers which are cholinergic. They obtained from the venous effluent of the hind foot of a cat, after sciatic stimulation, an acetylcholine-like substance.

That sweating, a parasympathetic response, occurs in states of increased sympathetic activity may at first seem confusing. "Breaking out in a cold sweat" is a common expression. This confusion may result from the arbitrary separation of the autonomic system into the parasympathetic and sympathetic divisions. This separation implies a reciprocity of action. According to Cannon[3] during emotional crises, such as in fright and rage, the sympathetic system tends to discharge *en masse*. It does not mean, however, that the parasympathetic system is inactive or inhibited. Gellhorn[8] has recently shown that emotional excitement evokes a stimulation of *both* branches of the autonomic nervous system, although under normal conditions the sympathetic system predominates. The principle of reciprocal innervation of both divisions of the autonomic nervous system is also not borne out on clinical grounds. It is practically impossible to find a pure example of vagotonia or sympathotonia. Thus a vagotonic individual may have a slow pulse but wide pupils. In hyperthyroidism there may be a rapid pulse, exophthalmus, and hyperglycemia; yet these patients often complain of diarrhea and moist palms.

XUM

It has not been sufficiently well appreciated that sweating of the palms differs from sweating on the general body surface. Anatomically, there are more sweat glands per square area in the palm than anywhere else in the body. Krause[14] found twice as many sweat glands per square

FIG. 2.—Sweat response of the dorsum of the hand in a patient with neuro-circulatory asthenia. Compare with Fig. 4.

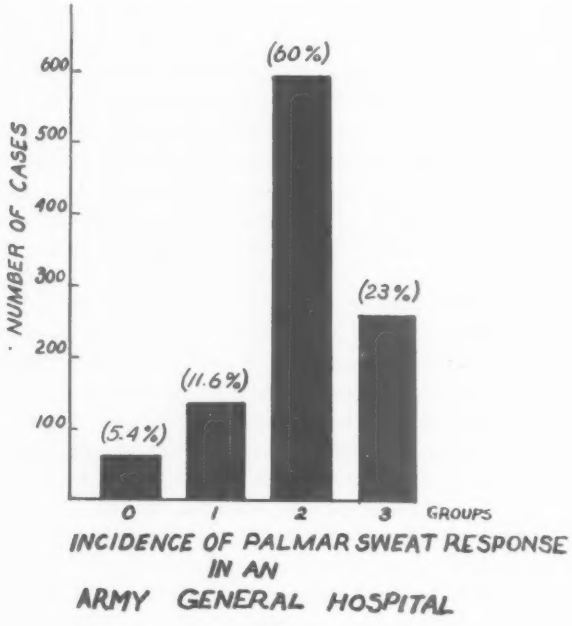


FIG. 3.

area on the palm as on the dorsal aspect of the hand, 4 times as many as on the chest, and over 5 times as many as on the back and buttock. The sweat glands on the palm are arranged in linear fashion on ridges. These ridges assume a characteristic pattern and are arranged in such

a way as to assure maximum grasping and tactile facility.[11] Functionally, the amount of perspiration on the palm is from 5 to 10 times as great as that of the general body surface.[15] Studied microscopically[12] the secretion of sweat on the palm and sole takes place continuously, whereas it is intermittent on the general body surface. Moreover, palmar sweating differs from that of the general body surface in that under ordinary conditions it is not influenced by outside temperatures.[15]

FIG. 4.—An example of excessive palmar sweating seen in a patient with neuro-circulatory asthenia.

Exposure of the body to a high temperature does not augment sweating of the palms. Experimentally it can be demonstrated that palmar sweating may be evoked by mental stimuli.[15] For instance, problems in simple arithmetic will cause a distinct and measurable increase in sweat confined to the palms and soles. In a relaxed state, such as in sleep, the palms are characteristically dry. Finally, the palm is one of the few places where emotional sweating takes place, and is peculiarly an indicator of emotional disturbances. In anxiety neurosis, where

autonomic phenomena are frequent, excessive sweating of the palms is seen[21] (Figs. 2 and 4).

By utilizing the galvanic skin reflex, palmar sweating has been studied extensively. A complete review of the subject has been given by Darrow.[7] However, the galvanic skin reflex study requires a complicated apparatus. Also, the apparatus used is not generally available to physicians, and is subject to technical errors.

To overcome these objections a colorimetric technique using impregnated paper was devised. A study of the palmar sweat response was made in over 1100 patients in an Army General Hospital[20] (Fig. 3). It was observed that a high percentage of these patients showed manifestations of a disturbed autonomic nervous system, one of the striking features of which was excessive palmar sweating. Approximately 25% of the patients showed a (3) response, and over 80% showed a combined (2) and (3) response. Invariably, in those patients who showed a (3) or intense response, evidence of emotional strain or a disturbance of the autonomic nervous system was present. These patients made poor soldiers and were hospitalized frequently. It is anticipated in the near future to study palmar sweating in well seasoned troops.

The clinical observation of excessive palmar sweating is not new. DaCosta[5] in 1871 in his classical paper on the "irritable heart" stated: "But there was also evidence of disorder of the sympathetic nervous system as shown in the itching of the skin and excessive perspiration from which many suffered. Inordinate sweating of the hand was several times complained of (as in case 159)." It is interesting to note that DaCosta advised the use of atropine which has later been shown to be a powerful antiparasympathetic drug. In an analysis of 200 cases of DaCosta syndrome, Wood[23] in 1941 found visible sweat on the palms in 67% of the patients. It is now generally agreed that in this disorder there are emotional disturbances as well as disturbances of the vegetative nervous system. Palmar sweating is merely one expression of these changes. Palmar sweating is such a constant and striking feature of neuro-circulatory asthenia that its presence should always be looked for as a point in diagnosis (Fig. 4).

Summary. 1. A test for the palmar sweat response has been devised which has several advantages over other methods previously used.

2. Various kinds of sweating are discussed.

3. The palmar sweat response was observed in more than 1100 patients and the clinical significance discussed.

4. Palmar sweating is unique and differs from general body sweating on anatomic and physiologic grounds. It attains special significance when it is looked upon as a cholinergic phenomenon related particularly to emotional activities.

REFERENCES

1. Bechterew, W.: Arch. Anat. Physiol. (physiol. abtheil.), p. 297, 1905.
2. Bieber, I., and Fulton, J. F.: Arch. Neurol. and Psychiat., **32**, 433, 1934.
3. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, 2nd ed., New York, Appleton, 1929.
4. Cushing, H.: Pituitary Body and Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Thomas, 1932.
5. DaCosta, J. M.: Am. J. Med. Sci., **61**, 71, 1871.

6. Dale, H. H., and Feldberg, W.: J. Physiol., **81**, 40, 1934; **82**, 121, 1934.
7. Darrow, C. W.: Arch. Neurol. and Psychiat., **37**, 641, 1937.
8. Gellhorn, E.: Autonomic Regulations, New York, Interscience, 1943.
9. Guttmann, L.: J. Neurol. Psychiat., **3**, 197, 1940.
10. Hermann, L., and Luchsinger, B.: Arch. f. d. ges. Physiol., **17**, 310, 1878.
11. Jones, F. W.: The Principles of Anatomy as Seen in the Hand, Baltimore, Williams & Wilkins, 1942.
12. Jurgensen, E.: Arch. klin. Med., **144**, 193, 1924.
13. Kennard, M. A., Viets, H. R., and Fulton, J. F.: Brain, **57**, 69, 1934.
14. Krause: Wagner's Handworterbuch der Physiologie, **2**, 131, 1844. (Cited by Kuno.)
15. Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, 1934.
16. Minor, V.: Deutsch. Ztschr. f. Nervenheilk., **101**, 302, 1927.
17. Rabiner, A. M.: Arch. Neurol. and Psychiat., **32**, 437, 1934.
18. Roth, G.: Proc. Staff Meet., Mayo Clin., **10**, 383, 1935.
19. Sanctorius: Medicina Statica, translated by John Quincy, 2nd ed., London, 1720.
20. Silverman, J. J., and Powell, V. E.: Palmar Sweating in an Army General Hospital (in press).
21. Solomon, A. P., and Fentress, T. L.: J. Nerv. and Ment. Dis., **80**, 163, 1934.
22. Wang, G. H., Pan, J. G., and Lu, T. W.: Chinese J. Physiol., **3**, 109, 1939.
23. Wood, P.: Brit. Med. J., **1**, 845, 1941.

THE VALUE AND LIMITATIONS OF THE CONGO RED TEST FOR AMYLOIDOSIS

By Marguerite G. Stemmerman, M.D.
ASSISTANT PATHOLOGIST
AND
Oscar Auerbach, M.D.
PATHOLOGIST
STATEN ISLAND, N.Y.

(From the Department of Pathology, Sea View Hospital, Staten Island, N. Y.)

For the past 11½ years the Congo red test has been used at our institution as a diagnostic aid in determining the presence of generalized amyloidosis. During this time the technique introduced by Bennhold[2] has been twice modified, first by Friedman and Auerbach,[3] and later by Taran.[6] The method used by the latter author has been adopted by the committee of Standard Laboratory Procedure of the American Trudeau Society.[1]

In this period there were 468 persons who at autopsy revealed varying degrees of amyloidosis. The etiologic factor in the production of amyloidosis was chronic pulmonary tuberculosis in all but 7 cases. Of the latter, 5 had lung abscesses, 1 bronchiectasis and 1 syphilis. Two hundred and forty-six of these had Congo red tests performed before death. With this opportunity to compare the results of the Congo red test with the findings at autopsy, evidence was accumulated to evaluate the test, to attempt to find the cause for false results, to study the effect of repeated Congo red tests in the same patient, and to determine if excretion of the dye in the urine is of aid in the diagnosis of the amyloid nephrotic syndrome.

Material. This study is based upon 446 autopsy cases in which Congo red tests were performed during life. Two hundred and forty-six revealed amy-

loidosis of varying degrees at autopsy; the remaining 200 were consecutive cases in which no amyloidosis was found in any of the organs.

There were 416 Congo red tests done on the 246 patients with amyloidosis (1.7 tests per patient); while there were 233 tests performed on the 200 patients without amyloidosis (1.2 tests per patient). The higher percentage of tests performed in the former group is explained by two factors: (1) when the Congo red test resulted in a 100% absorption, as was the case in most individuals with amyloidosis, it provoked repetition of the test for verification; (2) the persons with amyloidosis in general had a longer duration of the pulmonary disease and, therefore, there was greater opportunity to repeat the test.

We[5] have previously established the standard that 90 or 100% absorption of the Congo red dye is to be considered a positive result. Harmon and Kernwein[4] prefer to make a diagnosis of amyloidosis only when the dye is completely removed from the blood after an hour (100%).

Comparison of Congo Red Test and Autopsy Findings Showing Amyloidosis. In Table 1 (A) the figures representing the percentage of Congo red absorption are based on the last test done during life, except for the 100% determinations. In the latter the first 100% determination is recorded.

In those cases with insufficient dye in the first specimen, the result is recorded as 100% absorption (14 cases). All of these patients at autopsy showed marked amyloidosis in at least 1 organ, and in 12 the liver parenchyma was almost completely replaced by amyloid. Therefore, the insufficient dye in the first specimen was probably not due to any "errors," discussed below, but rather due to the rapid absorption of the dye by parenchymal amyloid before the first (standard) specimen of blood was procured. The fact that most patients with marked amyloidosis at autopsy showed Congo red tests of insufficient dye alternating with 100% absorption on subsequent examinations supports this contention.

In 25 of 103 cases (24.3%) in which the test was performed 2 months or less before death, there was less than 90% absorption of the dye. This represents a false negative result.

In 86 of the entire group of 246 cases there was less than 90% absorption, a false negative diagnosis of 30.9%. Since, however, in many the amyloid was probably deposited after the test was performed, all the false negative results cannot be attributed to defects in the test.

Comparison of Congo Red Test and Autopsy Findings Showing no Amyloidosis. In Table 1 (B) the figures representing the percentage of Congo red absorption are based on the last test done during life. In all instances the test was performed 6 months or less before death. In those cases with insufficient dye in the first specimen, the test is recorded as 100% absorption (8 cases). The insufficient dye was probably due to one or more of the technical "errors" listed below, since repetition of the test, unlike the repetition in the amyloid group, failed to reveal 100% absorption.

Five of 119 cases in which the Congo red test was done 2 months or less before death showed 90 to 100% absorption, a false positive result of 4.2%. Thirteen of 200 cases in which the Congo red test was performed 6 months or less before death showed 90 to 100% absorption, a false positive result of 6.5%.

XUM

It is possible that a 100% absorption reported 5 to 6 months before death may represent small amounts of amyloid that resorbed prior to death. We do not have sufficient data to confirm this point.

TABLE 1.—PER CENT ABSORPTION OF CONGO RED IN AMYLOID AND NON-AMYLOID CASES

Interval before death	39% or less	40 to 49%	50 to 59%	60 to 69%	70 to 79%	80 to 89%	90 to 99%	100%	Total
A. *Amyloid*									
2 wks. or less	1	0	1	3	0	0	2	23	30
3–4 wks.	1	1	3	3	2	2	3	17	32
5–8 wks.	0	1	1	4	1	1	5	28	41
2½–4 mos.	5	4	6	2	0	0	1	19	37
5–6 mos.	3	4	1	0	3	1	5	9	26
7–12 mos.	3	5	5	2	0	0	0	18	33
12 mos.–2 yrs.	3	2	2	2	1	1	1	14	26
Over 2 yrs.	0	0	2	2	1	1	1	14	21
B. *Non-amyloid*									
2 wks. or less	7	4	10	6	8	2	1	3	41
3–4 wks.	12	1	12	4	4	2	0	0	35
5–8 wks.	13	3	11	7	7	1	0	1	43
2½–4 mos.	9	8	14	8	6	3	0	2	50
5–6 mos.	10	1	4	7	2	1	3	3	31

TABLE 2.—CHANGES IN PER CENT ABSORPTION IN REPEATED TESTS

Interval between tests	No change			Less absorptions				Greater absorption			
	100%	90 to 99%	Below 90%	90% to below	10 to 90%	100 to below 90%	Below 90%	Below 90 to 90%	90 to 100%	Below 90 to 100%	Below 90%
4 wks. or less	6	1	0	0	0	1	0	0	1	1	0
6 wks.	4	0	0	0	0	0	1	0	0	0	0
8–10 wks.	3	0	1	1	0	0	0	0	1	2	1
12 wks.	3	0	1	0	0	0	0	1	1	0	0
4 mos.	4	0	2	1	1	0	0	0	0	1	0
5 mos.	8	0	0	0	1	0	0	1	0	0	1
6 mos.	3	0	0	0	0	0	1	0	1	4	2

Sources of Error. The results of the Congo red test (Table 1) show that there are many more false negative than false positive reports. The possible sources of error may be either technical or physiologic. In general the technical errors are dependent upon whether or not the first (standard) specimen is too light or too dark. If too dark, the test may be falsely negative, when there are only small amounts of amyloid in the tissues. In this case, there is not sufficient absorption of dye to alter appreciably the highly concentrated standard. If the first specimen is too light the test may be either wrongly negative or positive, usually the latter.

The first specimen may be too dark, if the patient is markedly undersized (children and emaciated adults) (Taran and Eckstein[7]), or if the same syringe is used for securing the first specimen as was used to inject the dye. The first specimen may be too light, if the patient is markedly oversized; if the dye is injected partially into the tissues or varying amounts are left in the syringe; or if the first specimen is taken longer than 4 minutes after the injection of the dye.

In those cases in which the technical errors have been eliminated, physiologic factors may explain the erroneous results. The test is not sufficiently delicate to detect minimal amounts of amyloid. In none of our cases did we obtain a positive result where there were small

amounts in the spleen alone with or without involvement of the blood-vessels of the liver; and in only a few cases where there were moderate amounts in the spleen. This constituted the source of error in 75% of our false negative results. If the dye is excreted unduly rapidly into the urine before the second specimen is procured, there may be a false impression of absorption.

If the amyloid is absorbed during the interval between 2 tests there may be an apparent erroneous report. In our series there were 7 cases in which this might have been a possibility. Since, however, at necropsy we found no evidence that amyloid was or ever had been present in the tissues, we have listed this as a false positive result.

Repetition of the Congo Red Test. It has been assumed previously that a Congo red test, repeated soon after the first, was valueless, since the amyloid in the tissues having already taken up the dye from the first test would not be prepared to absorb that from the second, unless additional new amyloid were laid down during the interval period. It has been more or less arbitrarily stated that there should be an interval of at least 3 months between tests. There were 24 repeat tests done at intervals of less than 3 months (Table 2). In 21 of these the absorption remained at the same level or showed increased absorption. There were 15 repeat tests at intervals of 6 weeks or less, in 13 of which the absorption was unchanged or increased. There were 10 tests repeated within 4 weeks, of which 9 tests were unchanged or increased.

The 3 cases in the entire group of 24 which showed diminished absorption when the test was repeated in less than 3 months were as follows: (1) A test which showed 100% absorption originally dropped to 75% when the test was repeated after 4 days. It returned again to 100% after a 10 month interval. (2) A test repeated in 6 weeks showed a drop from 55% to 40%. When the test was repeated $8\frac{1}{2}$ months later it revealed a 95% absorption. (3) The test repeated after $2\frac{1}{2}$ months showed a drop from 90 to 60%. Since death occurred 2 years after the last test, amyloid may not have been present when either of the tests was performed.

In the group of non-amyloids with 20 repeat tests, a false positive result was never found twice on the same patient, with 1 exception. This person had 4 tests at about monthly intervals as follows: 100%, 50%, 100%, 10%.

Although the series of 44 cases is small, it may be concluded that the Congo red test can be repeated in 4 weeks or more, and reasonably safely in 2 weeks. Repeated tests will weed out the false positives, since in a true amyloid once 100% absorption always 100%. In the non-amyloids this is unlikely.

Excretion of Amyloid in the Urine. The urine was tested for the excretion of Congo red within 1 hour after injection in about 75% of all the cases. Normally the dye is ultimately excreted in the urine, but it is only in the presence of renal tubular damage that it is excreted within the first hour (Harmon and Kernwein[4]). In only 1 non-amy-

loid case was there such excretion, the absorption being 45%. This patient had a nephrotic syndrome, which was not, however, on an amyloid basis.

In 13 of the amyloid cases there was an excretion in the urine. In 1 of these, 2 of 6 tests showed excretion of the dye. In 5 of the 13, the second or third tests failed to reveal excretion. In 11 cases there was evidence of renal damage with large amounts of albumin, casts, red blood cells and white blood cells in the urine and slight to marked edema present at the time the test was performed. In all but 2 instances the test revealed 100% absorption, not only on this but on subsequent or previous tests.

At autopsy it was found that 5 cases died of uremia and 6 of progressive pulmonary tuberculosis with clinical and pathologic signs of pre-uremia. In 77 cases, in addition to these 11, there were well-marked nephrotic syndromes, and the patients ultimately succumbed in uremia and pre-uremia. In none of these was there excretion of the dye.

In 2 cases there was no evidence of renal disturbance, either clinically or pathologically, either at the time that the test was done or at autopsy 10 or 14 months later. The tests both showed 50% absorption.

Therefore, while the dye may be excreted in nephrotic syndromes, it is apparently adequately withheld by the kidney when the nephrosis is on an amyloid basis. A low renal threshold for that particular substance may be the explanation why, without any renal pathology, the dye is excreted.

Conclusions. The results of 649 Congo red tests for amyloidosis performed on 446 patients have been reviewed in order to evaluate the test and to determine the sources of error. It has proved to be a valuable procedure, in spite of a certain proportion of erroneous results, which in our series has been calculated as 24.3% false negatives and 4.2% false positives.

The sources of error have been enumerated. The presence of only minimal amounts of amyloid is the principal reason for false negative results, while technical errors are probably the chief cause of false positive reports. The latter may be eliminated by repetition of the test at an appropriate interval, which we have shown should be 1 month or more.

The determination of the presence of Congo red in the urine within 1 hour after injection of the dye has been of little value in the diagnosis of amyloid nephrosis.

REFERENCES

1. American Trudeau Society: Am. Rev. Tuberc., **45**, 103, 1943.
2. Bennhold, H.: Deutsch. Arch. f. klin. Med., **143**, 32, 1923.
3. Friedman, M., and Auerbach, O.: J. Lab. and Clin. Med., **21**, 93, 1935.
4. Harmon, P. H., and Kernwein, G.: Arch. Int. Med., **70**, 421, 1942.
5. Lipstein, S., and Auerbach, O.: Quart. Bull. Sea View Hosp., **2**, 120, 1937.
6. Taran, A.: Jour. Lab. and Clin. Med., **22**, 975, 1937.
7. Taran, A., and Eckstein, A.: Am. J. Med. Sci., **203**, 246, 1942.

XUM

CREATINURIA IN HYPERTHYROIDISM AND IN ESSENTIAL HYPERTENSION

By Jerome V. Treusch, M.D.
FELLOW IN MEDICINE, MAYO FOUNDATION

Edwin J. Kepler, M.D.
DIVISION OF MEDICINE

Marschelle H. Power, Ph.D.
DIVISION OF BIOCHEMISTRY

AND

Samuel F. Haines, M.D.
DIVISION OF MEDICINE
MAYO CLINIC, ROCHESTER, MINN.

The increase of urinary creatine in many cases of exophthalmic goiter was first reported by Shaffer[11] in 1907. He found it in 8 of 12 cases studied. In 1931 Kepler and Boothby[6] summarized the literature to that time on creatinuria in hyperthyroidism and reported that in exophthalmic goiter the incidence of creatinuria was 61%, in adenomatous goiter with hyperthyroidism 63%, while in their control groups it was only 9% among males and 23% among females. They concluded that creatinuria could be considered a "fairly common and characteristic phenomenon of hyperthyroidism." Palmer[8] showed that in those cases of hyperthyroidism in which the creatine content of the urine was increased definitely, the creatinuria decreased after the administration of iodine. Richardson and Shorr,[9,10] who have felt, contrary to the conclusions of many other workers, that urinary excretion of creatine could be used as a clinical sign of value in hyperthyroidism, recommended a creatine tolerance test in addition to determinations of spontaneous excretion of creatine as giving a still more accurate method of indicating the correlation with hyperthyroidism. Thorn,[13] using Richardson and Shorr's method of performing the creatine tolerance test, with a slight modification, reported a high degree of correlation between the results of this test and hyperthyroidism; but Sohval, King and Reiner,[12] using Richardson and Shorr's method, reported findings which did not confirm these results. They, therefore, doubted the clinical value of the test. In 1939 Wang[15] reviewed completely the subject of creatine metabolism and reported additional clinical and experimental investigations. Wang concluded that in hyperthyroidism the urinary excretion of creatine usually is increased, but that this is not definite nor specific enough to be of value clinically.

Two facts are generally recognized: (1) that most normal adults, especially men, do not excrete significant amounts of creatine in their urine, and (2) that increased creatinuria occurs in several conditions other than hyperthyroidism such as the muscular dystrophies, acute anterior poliomyelitis, febrile states, the postpartum state, and so forth.

Recently, Tierney and Peters,[14] using a new sensitive method employing the photo-electric colorimeter, correlated the levels of creatine

XUM

in the blood serum with those in the urine of normal adults and of hyperthyroid patients. They found that creatine acted like a threshold substance, appearing in the urine whenever the blood level exceeded 0.58 mg. per 100 cc. They also performed creatine tolerance tests and determined that, after the ingestion of creatine, the usually high serum creatine and the creatinuria of the patient who had hyperthyroidism were increased more proportionately than those of the normal adult.

That an increase in the basal metabolic rate occurs in many cases of essential hypertension has been observed by many workers in the past 20 years. Furthermore, in spite of the increased metabolism and some rather marked resemblance of symptoms at times to hyperthyroidism, many of these patients have been demonstrated not to have hyperthyroidism.

Mountain, Allen and Haines[7] analyzed 827 cases of essential hypertension from the Mayo Clinic from the standpoint of the basal metabolism and thyroid status. They reported a basal metabolic rate greater than +15% in 7% of the cases of hypertension in Groups 1 and 2, in 12% of the cases of hypertension in Group 3, and in 27% of cases in Group 4.* They felt that the elevated basal metabolic rate, found in many cases of hypertension was not dependent on a disturbance in thyroid function.

From the standpoint of circulatory dynamics, Weiss[16] has pointed out that the pulse rate, velocity and amount of blood flow are not increased in proportion to the metabolism in cases of arterial hypertension and increased metabolism, in contrast to the picture in the usual case of hyperthyroidism.

Crile and McCullagh[3] reported on levels of iodine in the blood in cases of essential hypertension and increased metabolism without hyperthyroidism. Levels of iodine in the blood in 11 such cases were normal in 5, slightly elevated in 3, and abnormally high in 3. Curtis,[4] however, showed that in hypertension, even without an elevated basal metabolic rate, there was not infrequently an inexplicable increase of iodine in the blood. Crile and McCullagh felt that a low level of iodine in the blood was nevertheless of value in ruling out hyperthyroidism.

Practically no determinations of urinary creatine have been reported in the literature to date on this specific group of patients who have hypertension and an elevated metabolic rate but without hyperthyroidism. Wang[15] analyzed 7 cases of hypertension, without regard to the basal metabolic rates, and found normal elimination of creatine in 6 cases and somewhat high elimination in 1 case. Sohval, King and Reiner[12] reported no creatinuria in 6 cases of hypertension, and in 4 of these the basal metabolic rate was +15% or more.

* At the clinic, cases of hypertension are divided into 4 groups, depending on the severity of the disease.[5] The severity of the hypertension is estimated to a large extent by the pathologic changes which can be seen in the ocular fundi. In hypertension Group 1, the changes in the retinal arterioles are minimal. In Group 2, the arteriolar changes are definite, but retinitis is not present. In Group 3, there are angiospastic changes, retinitis and pronounced sclerotic changes in the arterioles. Group 4 is characterized by edema of the optic disk in addition to the changes that are present in Group 3.

The present study was undertaken with a double purpose in mind: (1) to reëvaluate creatinuria as a sign of hyperthyroidism especially as it may help in ruling in or out hyperthyroidism in cases of hypertension with elevated basal metabolic rates, and (2) to ascertain if any difference occurs in these 2 groups of cases, which, even if not helpful in clinical differentiation, might serve as supportive evidence to that already accumulated that the elevated basal metabolic rate in some cases of hypertension is on a different basis from that in hyperthyroidism.

TABLE 1.—COMPARISON OF RESULTS

		Excretion of creatine in 24 hours					
		Less than 90 mg.		90 to 135 mg.		More than 135 mg.	
	Patients	Patients	%	Patients	%	Patients	%
Exophthalmic goiter	29	4	14	5	17	20	69
Males	17	4	..	3	..	10	..
Females	12	..	..	2	..	10	..
Adenomatous goiter with hyperthyroidism	10	2	20	2	20	6	60
Males	4	1	..	2	..	1	..
Females	6	1	..	..	..	5	..
Adenomatous goiter without hyperthyroidism	6	5	83	0	..	1	17
Females	6	5	..	..	..	1	..
Hypertension (B.M.R. +15 per cent or more)*	18	12	66	3	17	3	17
Males	10	9	..	..	..	1	..
Females	8	3	..	3	..	2	..
Hypertension (B.M.R. less than +15 per cent)	17	11	65	5	29	1	6
Males	11	7	..	4	..	..	..
Females	6	4	..	1	..	1	..
Total cases of hypertension	35	..	66	..	23	..	11
Total cases of hyperthyroidism	39	..	15	..	18	..	67

* Clinically not hyperthyroidism.

Material and Methods. In order to make the test as simple and practical as possible, no special dietary restrictions were imposed. In this respect our data may be compared to those of Wang,[15] and Brøchner-Mortensen and Møller,[1,2] whose patients were allowed to receive the regular hospital diet. Samples of urine for 12 or 24 hours were collected as accurately as possible. In many instances 2 or 3 successive 24-hour specimens were obtained. Creatine was determined according to the method of Folin, after conversion to creatinine by boiling with picric acid solution. The values are calculated on the basis of the total output of creatine in 24 hours and are expressed in milligrams.

Our cases included 29 cases of exophthalmic goiter before any compound solution of iodine (Lugol's solution) had been given, 10 cases of adenomatous goiter with hyperthyroidism, 6 cases of adenomatous goiter without hyperthyroidism and 35 cases of essential hypertension, in 18 of which the basal metabolic rate was elevated to +15% or more.

The ages of the patients varied as follows: from 17 to 59 years for those having exophthalmic goiters; from 23 to 64 years for those having adenomatous goiter with or without hyperthyroidism, and from 25 to 63 years for those having hypertension.

In all but 5 of our 29 patients who had exophthalmic goiter, subtotal thyroidectomy was performed at the clinic, and the removed thyroid tissue showed on histologic study the confirmatory findings of diffuse parenchymatous hypertrophy.

The cases were grouped according to whether the creatine excreted in the urine was less than 90 mg. in 24 hours, 90 to 135 mg. in 24 hours, or more than 135 mg. in 24 hours.

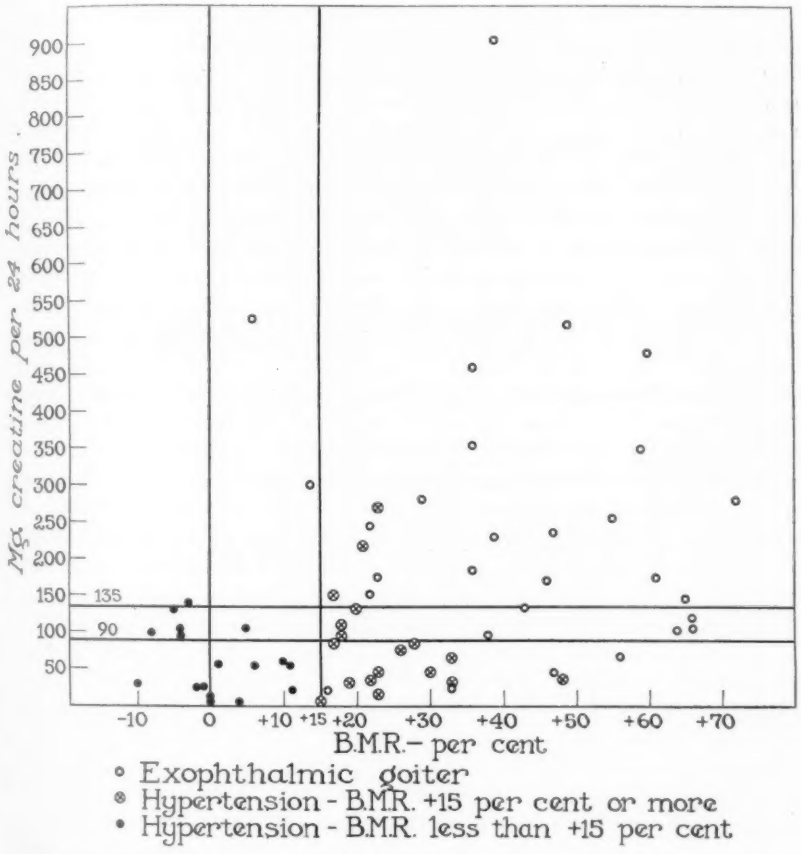


FIG. 1.—Comparison of basal metabolic rates and urinary excretion of creatine in cases of exophthalmic goiter and hypertension. Of the 3 patients having hypertension and basal metabolic rates greater than +15% and more than 135 mg. of creatine in the urine, 2 were women, aged 46 and 48 years, and 1 was a man, aged 36 years.

Results. Of the 29 patients who had exophthalmic goiter, 20 (69%) excreted more than 135 mg. of creatine in 24 hours, 5 (17%) excreted 90 to 135 mg. and 4 (14%) excreted less than 90 mg. Of 10 patients with adenomatous goiter with hyperthyroidism, 6 (60%) excreted more than 135 mg. of creatine in 24 hours, 2 (20%) excreted from 90 to 135 mg. and 2 (20%) excreted less than 90 mg. (Table 1). The sex distribution of the patients has been indicated in Table 1. It is

seen that the totals were fairly evenly divided between the sexes, but that the differences in the results by sex were not large enough for any definite conclusions to be drawn on this basis.

Of 18 hypertensive patients whose basal metabolic rates were +15% or more, 12 (66%) excreted less than 90 mg. of creatine per 24 hours, 3 (17%) excreted from 90 to 135 mg. and 3 (17%) excreted more than 135 mg. Similarly, of 17 hypertensive patients whose basal metabolic rates were less than +15%, 11 (65%) excreted less than 90 mg. of creatine per 24 hours, 5 (29%) excreted between 90 and 135 mg. and 1 (6%) excreted more than 135 mg. (Table 1). In these 2 groups of hypertensive patients, the excretion of creatine is obviously similar, regardless of elevation of the basal metabolic rate. It might be pointed out further that, in the cases of hypertension in general, the results did not differ much from those which would be expected in a random group of normal adults of both sexes without hypertension. In Table 1, also, the percentage of cases of hyperthyroidism and of hypertension in each range of excretion of creatine are presented together for ready comparison. It is seen that, in the majority of cases of hyperthyroidism, whether it was associated with exophthalmic goiter or adenomatous goiter, more than 135 mg. of creatine was excreted in 24 hours; whereas in the majority of cases of hypertension, either with or without an elevation of the basal metabolic rate, less than 90 mg. of creatine was excreted in 24 hours. These findings are illustrated in Figure 1 which shows that although, in general, patients who have exophthalmic goiter excrete more creatine than the hypertensive patients with or without an elevated basal metabolic rate, there is no direct proportionality between the creatine content of the urine and the basal metabolic rate, even in the hyperthyroid patients considered alone.* The wide scattering of the results, as seen on the graph, limits markedly the value of spontaneous creatinuria as a clinical sign in these conditions, but these figures certainly are consistent with the opinion that the elevated basal metabolism in essential hypertension rests on a different physiologic basis than that in hyperthyroidism.

Summary. Values for urinary creatine have been determined in cases of hyperthyroidism and in cases of essential hypertension with or without an elevated basal metabolic rate. Under the conditions of our study the majority of patients who had hyperthyroidism excreted more than 135 mg. of creatine in 24 hours, whereas the majority of patients who had essential hypertension even with an elevated basal metabolism excreted less than 90 mg. of creatine in 24 hours.

Conclusions. 1. The wide scattering of the results limited markedly the value of spontaneous creatinuria as a clinical sign for ruling hyperthyroidism in or out in cases of essential hypertension with elevated basal metabolism.

2. The results in general tended to substantiate the opinion that the elevated basal metabolism in essential hypertension rested on a different physiologic basis than that in hyperthyroidism.

* This point has been stressed by Kepler and Boothby[6] and Brøchner-Mortensen and Møller,[1,2] as well as others.

REFERENCES

1. Brøchner-Mortensen, K., and Møller, E.: Acta med. Scandinav., **102**, 417, 1939.
2. Brøchner-Mortensen, K., and Møller, E.: Acta med. Scandinav. (Suppl.), **123**, 180, 1941.
3. Crile, G., Jr., and McCullagh, E. P.: Med. Clin. North America, **24**, 395, 1940.
4. Curtis, G. M., and Cole, V. V.: Trans. Am. Assn. Study of Goiter, p. 142, 1934.
5. Keith, N. M., Wagener, H. P., and Barker, N. W.: Am. J. Med. Sci., **197**, 332, 1939.
6. Kepler, E. J., and Boothby, W. M.: Am. J. Med. Sci., **182**, 476, 1931.
7. Mountain, G. E., Allen, E. V., and Haines, S. F.: Am. Heart J., **26**, 528, 1943.
8. Palmer, W. W., Carson, D. A., and Sloan, L. W.: J. Clin. Invest., **6**, 597, 1929.
9. Richardson, H. B.: Med. Clin. North America, **18**, 791, 1934.
10. Richardson, H. B., and Shorr, E.: Trans. Assn. Am. Phys., **50**, 156, 1935.
11. Shaffer, P.: J. Biol. Chem. (Proc.), **3**, xiii, 1907.
12. Sohval, A. R., King, F. H., and Reiner, M.: Am. J. Med. Sci., **195**, 608, 1938.
13. Thorn, G. W.: Endocrinology, **20**, 628, 1936.
14. Tierney, N. A., and Peters, J. P.: J. Clin. Invest., **22**, 595, 1943.
15. Wang, E.: Acta med. Scandinav. (Suppl.), **105**, 7, 1939.
16. Weiss, S.: New England J. Med., **207**, 165, 1932.

THE EFFECT OF CALCIUM PANTOTHENATE AND PARA-AMINOBENZOIC ACID ON GRAY HAIR IN MAN

A Study on a Group of Young and Older Individuals

By Harold Brandaleone, M.D.

Elizabeth Main, M.D.

and

J. Murray Steele, M.D.

New York, N. Y.

(From the Third [New York Univ.] Medical Division, Goldwater Memorial Hospital, New York City, and the Department of Medicine, New York Univ.)

Reports of the effect of calcium pantothenate and paraaminobenzoic acid* on the color of gray hair in man or animals, have been confusing as to which of the two drugs is the more important; whether both are necessary or, in the case of man, whether an unquestionable effect has ever been observed. In this paper an attempt is made to clarify this state of affairs by the addition of new data as well as by a brief discussion.

It has been reported[10,11,16–19,21] that a deficiency of the filtrate factor of the vitamin B complex is accompanied by graying of fur in rats and dogs. The administration of the filtrate factors plus other vitamin B factors apparently helped to darken the fur in some animals.

Morgan, Cook, Davison and Simms[10,18] first noted that the substance active in curing graying, is contained in the filtrate fraction of vitamin B_2 complex, *i. e.*, it is in the water extract of yeast, lime or rice bran after thiamin, pyridoxine and riboflavin have been removed. These investigators also found that supplying this filtrate fraction cured grayness of fur in animals. Ralli, Clarke and Kennedy,[25] found that

* Calcium pantothenate will be referred to as Ca.P., paraaminobenzoic acid as PABA, and pantothenic acid as P.A.

animals with low salt intake developed graying of fur much sooner than those on high salt intake.

In 1940, Gyorgy, Poling and Subbarrow[9] observed that crude concentrates of P.A. had a definite curative effect on nutritional achromotrichia in rats. However, the fur did not become completely black in most instances, and depigmented areas often persisted. Williams[33] failed, however, to find any preventive or curative effect in gray hair in rats when P.A. was added. Frost, Moore and Dann[7] reported that certain liver extracts containing P.A. cured or prevented nutritional achromotrichia in rats, while synthetic Ca.P. had a negligible effect.

Evidence that P.A. was not the only factor in the graying of hair began to appear.[7,9,20,21] Martin, Wisinsky and Ansbacher[15] stated that PABA modifies melanin and that Ca.P. has no influence.

Ansbacher[1] reported that PABA was a factor in the prevention of achromotrichia in the rat, and a growth promoting factor for the chick. By means of this vitamin, he was able to overcome apparent grayness of the hair of rats, while another group of rats not given this vitamin continued to show typical achromotrichia. Martin and Ansbacher[13,14] confirmed the previous evidence that PABA has antigray hair activity in rats and mice. Unna, Richards and Sampson[32] and Emerson[4] found PABA ineffective for controlling achromotrichia in animals, but that P.A. and Ca.P. were beneficial in curing and preventing gray hair in laboratory animals.

Investigation of the effect of Ca.P. and PABA on human patients with gray hair followed these studies in animals. Punnett and Bader[23] gave 10 to 20 mg. of Ca.P. for from 1 to 6 months to 25 men and women, and in some cases supplemented this with the whole vitamin B complex. They obtained favorable results in a large proportion of cases. Sieve[27] reported beneficial effects after the administration of PABA to patients with definite achromotrichia. In 30 cases, PABA was given alone; in 20 cases, estrogenic hormones were administered at the same time. He observed marked darkening of hair within 2 months, and recommended 200 mg. of PABA daily as a reasonable therapeutic dose. Sieve and Ansbacher[29] reported the restoration of color of gray hair in more than 300 persons of both sexes after using 50 to 600 mg. of PABA a day. In a later paper[28] Sieve reported 800 cases with noticeable return of color to gray-haired individuals after treatment for 3 to 8 weeks. Since these results have been questioned,[2,24] it was believed that the present studies should be reported.

Procedure. Three groups of patients were studied. The first group, 19 elderly (over 55 years of age) males and females with white or graying hair, was selected from the wards of the 3rd Medical Division of Goldwater Memorial Hospital, where they were confined with a chronic disease, such as rheumatoid arthritis, arteriosclerosis with hemiplegia or Parkinsonism. No significant change in the basic disease of this group was noted throughout the study.

Eight young normal females (either nurses or internes, 29 to 38 years of age) with gray or graying hair, comprised the second group. These individuals were not patients. The first group was subdivided into 3 sub-groups; 7 persons

received 100 mg. Ca.P. plus 50 gm. of brewer's yeast; 5 persons received 200 mg. of PABA plus 50 gm. of brewer's yeast daily; the remaining 7 received 100 mg. Ca.P., 200 mg. of PABA and 50 gm. of brewer's yeast daily.* The first group continued their medication for 8 consecutive months. In the second group, 6 persons received 100 mg. Ca.P., 200 mg. of PABA and 50 gm. of brewer's yeast daily (1 was irregular); while 2 received just the 100 mg. Ca.P. and the 200 mg. of PABA daily. They remained under treatment for 6 consecutive months.

The third group consisted of 6 normal white females, whose ages ranged from 33 to 42 years. This group was observed by Dr. Elaine P. Ralli at the Metabolism Clinic of the New York University College of Medicine Clinic. The patients were all prematurely gray, and the gray hair had been present for 10 to 15 years. They were given 20 mg. Ca.P. plus 3.5 gm. of yeast concentrate daily for periods of 6 to 10 months.* Photographs were taken at the beginning and end of the experiment, and hair samples were taken at monthly intervals. These were observed by Dr. Ralli at least every 4 weeks. There was no apparent ill-effects from any of the drugs, except for occasional nausea which was probably due to the yeast.

In Groups 1 and 2, at the beginning of the experiment, photographs of the head and samples of hair from a given area were taken from each subject. This was repeated in the middle and at the end of the experiment. Color photographs of the hair samples of selected individuals were taken later. In addition, the same two observers saw these patients at least every 4 weeks and notations were made. At the end of the experiment, the photographs, samples of hair and opinions as to change in color were compared.

Results. Seventeen subjects failed to exhibit any change (Class I); 14 showed such slight change that its existence and certainly its value to the patient was doubtful (Class II); 2 patients exhibited definite change (Class III).

The photographs of the head were useless because slight changes in distance or lighting made large differences in the apparent color of hair. Hair samples were valuable in discrediting many subjectively favorable notes; a very definite color change must occur before it is apparent in the clippings.

Several changes were noted, (Table 1). The most common was the appearance of a yellow or greenish cast to the gray hair, that usually appeared during the first few months and did not always persist. The next most frequent change was the new growth of scattered wiry black hairs. In several cases there was thought to be an increased luster without actual change in color. In one man (Case No. 18), whose hair was sparse, there was an increase in the number of hairs. In only 2 patients (Cases 5 and 6) was there a significant change in color. Both of these patients were males and suffered from rheumatoid arthritis. Both had had brown hair, the one a red-brown, the other a yellow-brown. Both men noticed the change themselves. The change which was observed tended toward a return to the original color. It became apparent after the drugs had been taken for a period of 2 to 3 months, therafter increasing slowly in intensity until the drugs were stopped. These men were both in the group that received PABA, Ca.P. and yeast.

* We are indebted to Merck & Co., Inc., through the office of Dr. D. F. Robertson for furnishing us with the Ca.P. and PABA necessary for this study, and to the Vitamin Food Co., Inc., for the brewer's yeast and photographs. The yeast concentrate used by Dr. Ralli was supplied by the Freeda-Agar Products Co., New York.

TABLE 1.—RESULTS OF EFFECT OF CALCIUM PANTOTHENATE AND PARAAMINOBENZOIC ACID ON THE GRAY HAIR OF HUMANS (OLDER GROUP)

Patient, age and sex	Medication	Objective change: Hair	Objective change: Picture	Subjective change	Class
1. J.H. 65 M.	Yeast Ca.P. PABA	? Darker	No change	Sl. incr. number hairs	II
2. H.H. 35 M.	"	Grayer	"	? Grayer	I
3. J.McL., 1 23 M.	"	No change	"	No change	I
4. R.R. 72 M.	"	"	"	"	I
5. J.Sch. 58 M.	"	Def. change to red-brown	"	Def. darkening along sides of part	III
6. A.S. 61 M.	"	Def. change to red-brown	"	Very def. red change	III
7. J.S. 62 M.	"	Sl. darker	"	Sl. late yellowing	II
8. M.M. 57 F.	Yeast PABA	Lighter than control	"	Early greenish change	II
9. R.McM. 61 F.	"	Whiter than control	"	Early scattering dark hair; then no change	II
10. M.N. 67 F.	"	No change	"	No change	I
11. P.T. 52 F.	"	"	"	Early dark streak over crown; then no change	II
12. F.D. 62 M.	"	"	"	? Scattering of dark hairs	II
13. T.O'T. 65 M.	Yeast Ca.P.	Lighter than control	? Darker	Sl. golden change	II
14. M.D. 58 F.	"	? Darker	No change	Sl. early yellowing	II
15. G.D. 68 F.	"	Def. yellow early; then return to control	"	Def., temporary, early yellowing	II
16. J.F. 85 M.	"	No change	"	No change	I
17. F.K. 66 M.	"	Sl. darker	"	Sl. increase number of dark hairs	II
18. J.McL., 2	"	? Darker	"	No color change, def. increase number of hairs	I
19. M.M. 73 M.	"	No change	"	No change	I

None of the younger subjects (Tables 2 and 3) showed a definite change. In 2 young women with pale red hair, there was an apparent but temporary deepening of the red color. The hair developed a yellow or greenish cast in some cases and there was some scattered new wiry black hairs seen, but the changes were not sufficient to be of practical value.

In the third group, none of the subjects exhibited any demonstrable change in the color of their hair; 2 subjects thought that their scalp was less scaly.

TABLE 2.—RESULTS OF EFFECT OF PABA AND CA.P. ON GRAY HAIR OF YOUNG WOMEN

Patient, age and sex	Medication	Objective change: Hair	Objective change: Picture	Subjective change	Class
1. M.C. 35 F.	PABA Ca.P.	None	Grayer*	Yel. tint early, ? more gray later	I
2. E.N. 35 F.	Yeast PABA Ca.P.	Grayer	...	No change	I
3. E.C. 33 F.	"	? Darker	...	Sl. more red early, no effect on gray	II
4. A.A. 33 F.	PABA Ca.P.	? Darker	...	Yel. tint early, sl. darkening at temp.	II
5. M.B. 36 F.	Yeast PABA Ca.P.	None	Grayer*	Yel. tint early, ? darkening of gray	II
6. M.H. 34 F.	"	Yel. tint	Grayer*	Red? more red	II
7. M.Kv. 29 F.	(Irreg.)	None	Grayer*	? Darkening	I
8. M.Kd. 38 F.	"	More gray	...	Sl. darkening	I

* Follow-up photographs taken with different lighting, etc., so that all hair appears much more gray.

TABLE 3.—RESULTS OF EFFECT OF CA.P. ON GRAY HAIR OF YOUNG WOMEN

Patient, age and sex	Medication	Duration of treatment	Objective change: Hair	Objective change: Picture	Subjective change	Class
M.B.M. 42 F.	20 mg. Ca.P., 3.5 gm. concent. yeast	10 months	Grayer	No follow up	None	I
S.S. 37 F.	"	10 "	No change	Darker ?	Scalp better, texture better, yellow gray	I
A.T. 35 F.	"	10 "	"	More gray	Scalp better, no change in color	I
M.M. 33 F.	"	6 "	"	No follow up	No change	I
M.L. 40 F.	"	10 " (irregular)	"	"	"	I
C.G. 38 F.	"	10 months	Grayer	No change	"	I

Discussion. That only 2 of the 33 persons with gray hair exhibited a definite return of previous color while taking PABA and Ca.P. is of interest for at least two reasons. It suggests that a deficiency of PABA or Ca.P. or both, can under certain circumstances be at least one factor in the development of gray hair. Which substance is responsible is not clear, since both drugs were given to the 2 individuals in which change was observed. After the medication was stopped, the hair gradually became grayer again, a fact which makes the observation secure. What is perhaps of more interest, is that the numerous failures lead one to the conclusion that, for the most part, graying of the hair is dependent on some other train of events.

Martin[12] believes that the ratio of PABA to P.A. is important. He feels a preponderance of PABA favors graying. Pfaltz[22] found that the addition of P.A. to the diet of rats deprived of this vitamin par-

tially restored gray color. She found that when PABA was added, the color was restored quicker. This investigator also found that Inosital enhanced the pigment-restoring properties of P.A., although Emerson and Evans[4] did not find that Inosital significantly improved results over Ca.P. alone. Sieve[29] pointed out a possible relationship between PABA and hormones in the graying of hair. Gerstl, Lustig and Goldfarb[8] indicated that sex had a definite influence in the incidence of nutritional achromotrichia in mice. Forbes[6] reported that estrogen implanted pellets produced local pigmentation of fur in albino rats, while testosterone dipropionate failed. All this work however, is in an early stage.

It is important also to point out that the indiscriminate use of PABA in humans may be followed by toxic reactions. Scott and Robbins[26] found PABA to be poisonous to mice and dogs and less toxic to rats. In dogs, oral doses greater than 1 gm. per kilogram of body weight may cause death. It has also been found[5,30,31] that PABA inhibits bacteria-static action of sulfonamide drugs, and should therefore not be given when it is necessary to use these drugs.

Conclusions. In a group of 19 elderly individuals with gray hair, only 2 exhibited a significant change in color during an 8 months period of administration daily of 100 mg. calcium pantothenate; 200 mg. paraaminobenzoic acid, and 50 gm. of Brewer's yeast. Both were men.

In a group of 8 younger individuals who received the same dosage for 6 months (2 of the 8 omitted Brewer's yeast), and in a group of 6 younger individuals who received 20 mg. calcium pantothenate and 3.5 gm. of concentrated yeast daily, none developed any decrease in the gray color of their hair.

REFERENCES

1. Ansbacher, S.: Science, **93**, 165, 1941.
2. Editorial: J. Am. Med. Assn., **118**, 302, 1942.
3. Emerson, G. A.: Proc. Soc. Exp. Biol. and Med., **47**, 448, 1941.
4. Emerson, G. A., and Evans, H. M.: Proc. Soc. Exp. Biol. and Med., **46**, 655, 1941.
5. Findlay, G. M.: Brit. J. Exp. Path., **21**, 356, 1940.
6. Forbes, T. R.: Endocrinology, **30**, 465, 1942.
7. Frost, D. V., Moore, R. C., and Dann, R. P.: Proc. Soc. Exp. Biol. and Med., **46**, 507, 1941.
8. Gerstl, B., Lustig, B., and Goldfarb, A. R.: Science, **96**, 447, 1942.
9. Gyorgy, P., Poling, C. E., and Subbarrow, Y.: J. Biol. Chem., **132**, 789, 1940.
10. Lunde, G., and Kringstad, H.: J. Nutr., **19**, 321, 1940.
11. Lunde, G., and Kringstad, H.: Ztschr. f. physiol. Chem., **257**, 201, 1939.
12. Martin, G. J.: *In* Science News Letter, **41**, 236, 1942.
13. Martin, G. J., and Ansbacher, S.: J. Biol. Chem., **138**, 441, 1941.
14. Martin, G. J., and Ansbacher, S.: Proc. Soc. Exp. Biol. and Med., **48**, 118, 1941.
15. Martin, G. J., Wisinsky, W. A., and Ansbacher, S.: Proc. Soc. Exp. Biol. and Med., **47**, 26, 1941.
16. Morgan, A. F.: Science, **93**, 261, 1941.
17. Morgan, A. F., Cook, B. B., and Davison, H. G.: J. Nutr., **15**, 27, 1938.
18. Morgan, A. F., and Simms, H. D.: J. Nutr., **19**, 233, 1940.
19. Morgan, A. F., and Simms, H. D.: J. Nutr., **20**, 627, 1940.
20. Nielsen, E., Olsen, J. J., and Elvehjein, C. A.: J. Biol. Chem., **133**, 637, 1940.
21. Oleson, J. J., Elvehjem, C. A., and Hart, E. B.: Proc. Soc. Exp. Biol. and Med., **42**, 283, 1939.
22. Pfaltz, H.: Ztschr. Vitaminforsh., *in* New York Times, Oct. 25, 1942.

XUM

23. Punnett, P. W., and Bader, M. E.: Good Housekeeping, February, 1942, p. 64; September, 1942, p. 63.
24. Queries and Minor Notes: J. Am. Med. Assn., **119**, 1536, 1942.
25. Ralli, E. P., Clarke, D. H., and Kennedy, E.: J. Biol. Chem., **141**, 105, 1941.
26. Scott, C. C., and Robbins, E. B.: Proc. Soc. Exp. Biol. and Med., **49**, 184, 1942.
27. Sieve, B. F.: Science, **94**, 257, 1941.
28. Sieve, B. F.: South. Med. and Surg., **104**, 35, 1942.
29. Sieve, B. F., and Ansbacher, S.: Drug. and Cosmetic Indust., **49**, 693, 1941.
30. Silbie, F. R.: Brit. J. Exp. Path., **21**, 90, 1940.
31. Spink, W. W., and Jermsta, J.: Proc. Soc. Exp. Biol. and Med., **47**, 395, 1941.
32. Unna, K., Richards, G. V., and Sampson, W. L.: J. Nutr., **22**, 553, 1941.
33. Williams, R. R.: Science, **92**, 561, 1940.

TIME–ACTIVITY CURVES OF GLOBIN INSULIN WITH CLINICAL APPLICATIONS

By Helen Eastman Martin, M.D.
INSTRUCTOR IN MEDICINE
D. G. Simonsen, Ph.D.
RESEARCH CHEMIST IN MEDICINE
AND
Noradeane H. Homann
RESEARCH TECHNICIAN IN MEDICINE
LOS ANGELES, CALIF.

(From the Department of Medicine, Univ. of Southern California School of Medicine, and the Department of Medicine of the Los Angeles County Hospital)

In the study of any new insulin preparation it is important to determine the total duration of action, and the activity per hour. The time-activity curve has proved a useful method for such study and has been described in detail in previous communications, with reference to regular and protamine zinc insulins.[4,6,7] In brief, after the injection of the dose of insulin to be studied, glucose is given by mouth at variable intervals in the amount required to keep the blood sugar within the physiologic range (80 to 120 mg. per 100 cc.) as determined by repeated blood sugar determinations. In the severe diabetic, with a fasting insulin requirement[8] the rise of the blood sugar when insulin effect is over gives a sharp end-point for the duration of action.

While several studies of globin insulin have appeared in the literature they have considered blood sugar curves in (1) the fasting state,[1] (2) with diet,[5,2] and (3) with constant 2-hourly feedings of glucose.[8] The present report is a study of the time-activity function of globin insulin, with the clinical application of the results to the optimum arrangement of the diet. The studies include: (1) a summary of 8 time-activity curves, with doses of globin insulin ranging from 10 to 80 units, (2) comparison of the time activity curves of the same dose of regular, protamine zinc and globin insulin in 2 patients, (3) globin insulin curves in 14 patients on a regular diet, and (4) out-patient progress records of 16 patients on globin insulin.

In the majority of instances, blood sugar determinations were made on oxalated venous blood by a modified Folin-Wu micro method.

Time-activity Curves. Figure 1 shows the activity of 80 units of globin insulin in a 14 year old white boy, a severe diabetic. The fall of the blood sugar from 251 to 116 mg. per 100 cc. in the first 5 hours of study, indicates a small insulin activity in the first few hours after

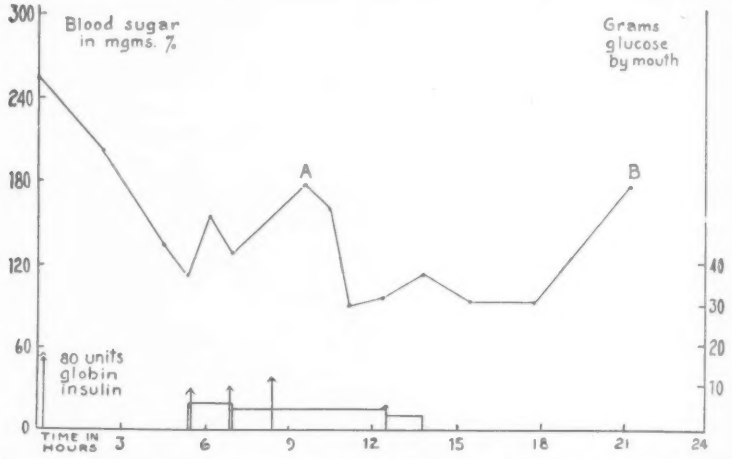


FIG. 1.—Time-activity curve 80 units of globin insulin. Point *A:* Too much glucose given at this point so blood sugar allowed to return to normal before next dose of glucose. Point *B:* End of appreciable activity. *Single tipped arrows* indicate amount of glucose given at that time, in all figures. *Boxes* represent the amount of glucose, calculated as grams per hour, in all figures. *Double tipped arrows* represent the time insulin was given, in all figures.

D. R. White male 14, No. 791–326. Diabetic of 1 year's duration. Severe diabetic in good control prior to test on regular insulin 50–30–30; protamine zinc insulin 35–0–0. Diet: C, 275; P, 100; F, 90. Preparation for test: Day before test, protamine zinc insulin was not given. Insulin day before test: regular insulin 50–30–20, and 20 at midnight, with a glass of milk, in addition to diet. No food day of test, except glucose by mouth as indicated in figure.

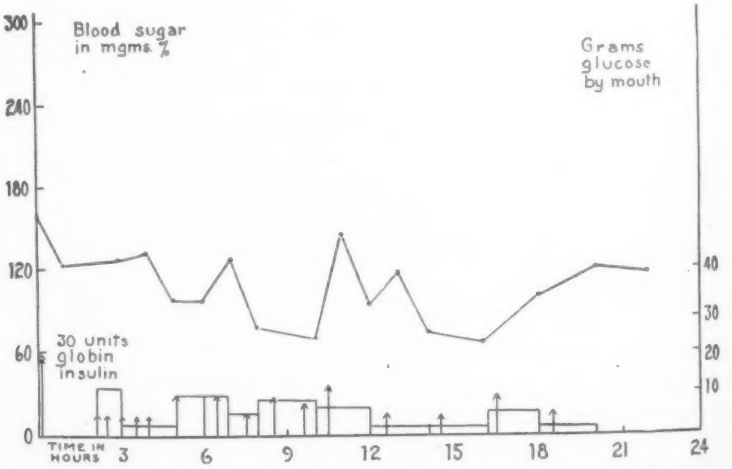


FIG. 2.—Time-activity curve 30 units of globin insulin. H. R. White male 57, No. 810–294. New, untreated diabetic. Controlled without insulin on diet: C, 150; P, 65; F, 80. Preparation for test: none. No food day of test, except glucose by mouth, as indicated in figure.

XUM

injection. From the 6th to the 13th hours, 37 gm. of glucose was given to balance insulin activity. At point *A* the amount given was in excess of the requirement, as indicated by the rise of the blood sugar. The peak activity is clearly between the 6th and 9th hours, as the largest amount of glucose was given in this period. The end of activity is sharp, with a rise of the blood sugar from 91 mg. per 100 cc. to 176 mg. per 100 cc. (point *B*), between the 18th and 21st hours after insulin injection. (No glucose was given by mouth after the 12th hour.)

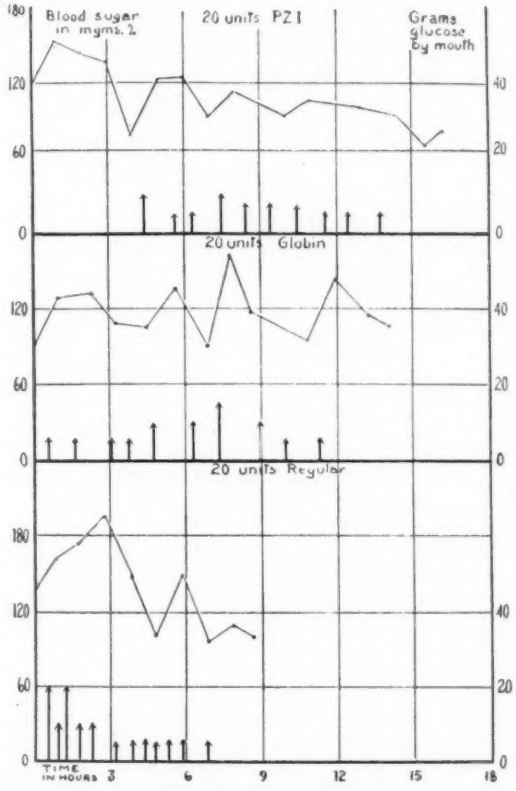


FIG. 3.—Comparison of the time-activity function of 20 units of regular, globin and protamine zinc insulin. Twenty units of regular, globin and protamine zinc insulin, respectively, given at 0 time on graph.

J. S. Mexican male 46, No. 679–103. Known diabetic 4 years. Well controlled on 30 units protamine zinc insulin. Diet: C, 175; P, 70; F, 80. Preparation for test: Day before each test protamine zinc insulin was discontinued and regular insulin 10–10–10 was substituted. No food day of tests, except glucose by mouth as indicated.

Figure 2 in contrast, shows the activity of 30 units of globin insulin in a 57 year old white male—a very mild diabetic. Although this patient was controlled on diet alone, this fact does not change the general configuration of the curve after the injection of insulin. Even non-diabetics can show peak points of action of injected insulin over and above the endogenous secretion. The total amount of glucose handled in any diabetic will depend not only upon the injected dose,

but upon the amount of the effective endogenous insulin. Ninety-five gm. of glucose was required to balance insulin activity, with the blood sugar level between 67 and 144 mg. per 100 cc. The peak of activity lies between the 5th and 10th hours. The end-point of activity is not clearly indicated, as the patient did not have a fasting insulin requirement. However, there is no appreciable effect after the 20th hour.

TABLE 1.—TIME-ACTIVITY FUNCTION OF GLOBIN INSULIN

Name	Usual insulin dose in units Diet C–P–F[1] in gm.	Dose of globulin insulin in units	Peak of action in hrs.	Duration of significant activity	Total gm. of glucose by mouth to balance activity	No. of hrs. of experiment
1. T. G. 62 Colored male No. 240–338[2]	10 PZI[3] 270–95–95	10	6–8	?	50	11
2. J. S. 45 Mex. male No. 679–103	30 PZI[4]	20	5–10	13+	75	14
3. J. S. 40 Mex. male No. 276–524	30 PZI 250–90–80	20	5–12	14+	90	15
4. H. B. 57 White male No. 810–294	No insulin 150–65–80	30	5–10	20	95	22
5. J. D. 17 White male No. 250–724	RI[3] 40–20–40 PZI 40 300–100–100	40	7–13	18+	95	21
6. D. S. 33 White male No. 631–831	RI 25–10–15 PZI 0–0–10 250–85–80	40	10–20 ?[5]	22+	127	22
7. W. H. 15 Colored female No. 597–734	RI 25–0–0 PZI 0–0–40 200–100–60	60	12–19 ?[6]	22+	20	22
8. D. R. 14 White male No. 791–326	RI 50–30–20 PZI 35 275–100–90	80	6–9	18	37	21

KEY: [1] C, carbohydrate; P, protein; F, fat in all tables.
[2] Permanent hospital file No.—in all tables.
[3] PZI, protamine zinc insulin; RI, regular insulin; CZI, crystalline zinc insulin—in all tables.
[4] PZI discontinued 24 hours before test with globin insulin in all patients except No. 1.
[5] Largest amounts of glucose given late (10th to 20th hour), with blood sugar of 30 mg. per 100 cc. at 18th hour.
[6] Difficult to tell peak as only 2 doses of glucose given—5 gm. at 6th hour and 15 gm. at 15th hour.

The activity of 20 units of globin insulin in a 46 year old Mexican male, a mild diabetic, is seen in Figure 3 (middle curve). During the first 4 hours after injection activity is present, as an hourly dose of 5 gm. of glucose caused little change in the blood sugar level. The peak

of activity occurs between the 5th and 10th hours. Activity is slight after the 13th hour. The blood sugar level fell only 10 mg. between the 13th and 14th hours, and no glucose was given after the 11th hour. This patient also shows no sharp rise of the blood sugar at the end of activity, as he is a mild diabetic with no basal insulin requirement.

Table 1 summarizes the results in the 8 patients on whom time-activity curves were run. The tests were conducted in similar fashion to those traced in Figures 1 and 2. In the majority of cases the peak of action occurred between the 6th and 10th hours, with the end of appreciable activity between the 14th and 18th hours.

Figure 3 shows the striking difference between the time-activity curves of regular, globin and protamine zinc insulins in the same patient. The regular insulin has its peak of action between the 1st and 4th hours, with the end of significant activity between the 7th and 9th hours. A total of 105 gm. of glucose was given to balance the insulin action. In contrast, the peak of action of the globin insulin is 5 to 10 hours, with little activity after the 14th hour. Seventy-five gm. of glucose were given to balance insulin activity. With the protamine zinc insulin the onset of appreciable activity is delayed, with the peak of action between the 7th and 11th hours. Some activity is still present at the 16th hour. Sixty-two and a half gm. of glucose were given to balance insulin activity.

Similar results were obtained in a second patient, in whom the time-activity curves with the same dose of regular, globin and protamine zinc insulin were made.

Blood Sugar Curves With Globin Insulin and Diet. Table 2 summarizes studies on 14 patients on their regular diets with one dose of globin insulin. Five or six blood sugar determinations were made throughout the 24-hour period: fasting, $1\frac{1}{2}$ to $2\frac{1}{2}$ hours after each meal, to obtain postprandial rises; and at 4 P.M. and midnight, for possible low points. Quantitative urine sugars* for the 24-hour period were also run. Seven of the patients received a mid-afternoon feeding, while 7 did not.

In general, the results show that the usual time of occurrence of hypoglycemia with globin insulin lies between 2 P.M. and midnight. Thus, 2 patients had blood sugar levels under 50 mg. per 100 cc. at 2 P.M.; 3 patients had blood sugar levels under 80 mg. per 100 cc. at 4 P.M.; 1 patient had a severe insulin reaction at 10:30 P.M.; and 3 patients had blood sugar levels under 65 mg. per 100 cc. at midnight. In only 1 patient was the fasting blood sugar level under 80 mg. per 100 cc., and no patients had insulin reactions between midnight and breakfast.

The majority of the patients showed a marked postprandial rise of the blood sugar after breakfast (67 to 124 mg. per 100 cc.) despite the fact that all the patients received a light breakfast—one-sixth to one-fifth of the total carbohydrate.

The milder diabetics (Cases 1, 4, 6, 7, 9, 10) showed fairly smooth 24-hour blood sugar curves, and were considered to be moderately well controlled, although certain adjustments of insulin and diet were

* Urine sugars were determined by the quantitative Benedict method.

TABLE 2.—GLOBIN INSULIN AND DIET

Name	Units globin[1] insulin	Diet C–P–F[2]	Blood sugar in mg. per 100 cc.						24 hr. urine sugar in gm.
			Fasting 1st day	1½–2½ hrs. after breakfast	1½–2½ hrs. after lunch	4–5 P.M.	1½–2½ hrs. after dinner	12 midnight	Fasting 2d day	
1. M. P. 13 White female No. 772–531	20	200–100–70[a]	109.0	106.0	47.0	...	132.0	99.0	...	0
2. L. K. 33 White female No. 314–400	20	200–75–80[a]	...	218.0[3]	274.0	166.0	...	...	99.0[3]	Not determined
3. E. R. 40 White female No. 605–164	20	200–75–80[a]	...	224.0	212.0	121.0	183.0	61.0	100.0[3]	Not determined
4. E. L. 30 A White female No. 162–277 B	20	100–60–40[c]	...	252.0	242.0	180.0	214.0[5]	97.0	86.9	21
	25	100–60–40[a]	...	194.2	190.4	60.0	...[4]	...	92.0	0
5. C. B. 5 White female No. 744–053	30	175–70–80[d]	...	206.0	80.0	46.0[6]	...	...	259.0	1+
6. J. S. 40 Mexican male No. 672–920	30	250–90–80[a]	67.0	148.0	182.0	...	150.4	103.6	...	0
7. J. S. 46 Mexican male No. 679–103	30	175–70–80[a]	82.0	129.0	138.0	...	143.9	127.4	...	0
8. C. S. 6 White female No. 798–777	30	175–80–75[f]	...	...	...	278.0	...	275.0	97.0	47
9. R. T. 35 Mexican male No. 820–719	30	300–90–80[f]	...	148.0	194.0	125.0	200.0	125.0	133.0	3

XUM

8. C. S. 6 White female No. 708–777	30	175–80–75[f]	...	...	...	278.0	...	275.0	97.0	47
9. R. T. 35 Mexican male No. 820–719	30	300–90–80[f]	...	148.0	194.0	125.0	200.0	125.0	133.0	3
10. J. M. 78 White male No. 753–322	35	150–60–80[a]	98.5	166.0	190.0	...	71.9	41.1	...	Not determined
11. E. D. 55 A White male No. 820–882 B	40	300–95–120[g]	...	416.0	198.0	119.0	127.0	56.0	240.0	16
	40	300–95–120[g]	347.6	421.2	41.0	...	105.0	81.0	333.0	32
12. J. D. 38 White female No. 238–170	40	225–80–70[f]	308.0	266.6	133.3	75.5	248.0	396.0	333.0	76
13. M. D. 83 White female No. 847–199	80	150–60–80[b]	...	236.6	261.4	224.8	338.0	250.0	119.0	Incontinent
14. P. A. 53 White female No. 825–066	80	130–100–120[a]	...	200.0	266.6	275.8	272.0	245.0	207.2	21

KEY:

[1] All patients except Nos. 6, 7, 8 on globin insulin at least 4 days before test.

[2] Arrangement of carbohydrate in diet:

- [a] 1/5 breakfast; 2/5 lunch; 2/5 dinner; with or without small bedtime feeding.
- [b] 1/6 breakfast; 1/3 lunch; 1/6 mid-afternoon; 1/3 dinner.
- [c] 1/6 breakfast; 1/3 lunch; 1/6 mid-afternoon; 1/4 dinner; 1/12 bedtime.
- [d] 1/6 breakfast; 1/3 lunch; 1/12 mid-afternoon; 1/3 dinner; 1/12 bedtime.
- [e] 1/5 breakfast; 1/3 lunch; 1/10 mid-afternoon; 2/5 dinner; ? bedtime feeding.
- [f] 1/5 breakfast; 1/5 lunch; 1/10 mid-afternoon; 2/5 dinner; 1/10 bedtime.
- [g] A—? arrangement, but interval feedings at 3 P.M. and 9 P.M.
  B—1/5 breakfast; 3/10 lunch; 1/10 mid-afternoon; 1/3 dinner; 1/10 bedtime.

[3] Just as breakfast finished.

[4] Severe insulin reaction requiring intravenous glucose at 10:30 P.M.

[5] 10 to 10:30 P.M.

[6] Afternoon feeding not eaten.

necessary to meet occasional low blood sugar points: 2 P.M., 4 P.M., and midnight.

Patients 2, 3 and 5 showed wider fluctuations of the blood sugar curve due to moderate, transient postprandial rise of the blood sugar curve.

In 4 severe diabetics (Cases 11, 12, 13, 14) control was very poor on one dose of globin insulin due to marked postprandial rises of blood sugar, and also low points in the afternoon or midnight, despite interval feedings. The globin insulin was not sufficient to control the fasting requirement in No. 11, as the blood sugar rose from 81 mg. per 100 cc. at midnight to 333 mg. per 100 cc. before breakfast. Patients 8 and 13, on the other hand, had a marked fall of the blood sugar from midnight to 6 A.M., even with marked postprandial hyperglycemia.

TABLE 3.—COMPARISON OF GLOBIN AND PROTAMINE ZINC INSULIN WITH DIET

Name	Insulin in units	Diet C–P–F[1]	Blood sugar in mg. per 100 cc.					24 hr urine sugar in gm.
			Fasting	2 hrs. after breakfast	2 hrs. after lunch	2 hrs. after dinner	Midnight	
1. M. P. 13 White female No. 772–531	35 PZI 20 Globin[2]	200–100–70 200–100–70	64.5 109.0	76 106	111 47	135.1 132.0	47.6 99.0	0 0
2. J. M. 78 White male No. 753–322	45 PZI 35 Globin[2]	150–60–80 150–60–80	74.0 98.5	158 166	164 190	198.1 71.9	121.1 41.1	Sl. tr. 0
3. J. S. 40 Mex. male No. 672–920	30 PZI 30 Globin[3]	250–90–80 250–90–80	67.0 80.0	148 150	182 173	150.4 220.0	103.6 92.6	? 0
4. J. S. 45 Mex. male No. 679–103	30 PZI 30 Globin[3]	175–70–80 175–70–80	82.0 133.0	129 200	138 142	143.9 121.0	127.4 80.6	0 0

KEY: [1] Arrangement of carbohydrate in diet: 1/5 breakfast; 2/5 lunch; 2/5 dinner; ? bed-time feeding.
[2] On globin insulin 5 days before test.
[3] On globin insulin 2 days before test.

Five patients (Nos. 1, 3, 4, 5 and 10) have been followed in the outpatient clinic for over 6 months, and have been in fair to moderate control during this period.

Four patients were studied on diet and protamine zinc insulin, and on globin insulin (Table 3). In 1 patient the dose of globin insulin was 15 units less than the protamine zinc insulin; and in another, 10 units less. In the other 2 patients, the same dose was used. In all 4 cases the fasting blood sugar level with protamine zinc insulin was lower by 13 to 51 mg. per 100 cc. than with globin insulin. In 3 of the patients on protamine zinc insulin, the lowest blood sugar of the 24-hour curve occurred fasting, in the other at midnight. The lowest peak of the globin curve occurred at midnight in 3 cases, and in the middle of the afternoon in the other. Except for the differences pointed out above, the general configuration of the curves was quite similar.

Table 4 summarizes the out-patient clinic records of 16 patients. Eight of these patients were in good or moderately good control, *i. e.*, excreted less than 10% of the carbohydrate intake in the 24-hour urine sample in three-fourths of the clinic visits. In this group the doses ranged from 10 units to 50 units of globin insulin. Five patients were in fair control (spilled less than 15% of the carbohydrate intake), with doses ranging from 20 to 80 units; 3 patients were in poor control (spilled over 20% of carbohydrate intake), with doses of 20 to 80 units of globin insulin, and 2 of these were taken off of globin insulin due to poor control. In certain instances poor control was due to intercurrent infections; in others to poor coöperation. Eleven of the 16 patients had been on 2 to 3 injections of insulin daily. Five of this group were in moderately good control on 1 injection of globin insulin. Three patients were given doses over 70 units; only 1 of these was in moderately good control.

Table 5 gives the time of occurrence of insulin reactions with globin insulin. Only 1 reaction occurred between midnight and 5 A.M. The largest number of reactions occurred between noon and 6 P.M.

Discussion. In accord with others[1,2,3,5] who have studied globin insulin, we have found that it is an insulin with prolonged activity (more than 18 hours), with a peak of action between 6 and 10 hours in the majority of patients.

It is obvious from the time-activity curves and studies on diet that the duration of appreciable effect, as with protamine zinc insulin,[3] is a function of the size of the dose and the severity of the diabetes—that is the amount of the hourly basal insulin requirement. Thus, Patient 8, Table 1, had an end of activity at 18 hours, with a dose of 80 units; while in another patient, No. 6, Table 1, 40 units lasted more than 22 hours. In the studies with diet, Patient 11, Table 2, on 40 units of globin insulin showed a marked rise of the blood sugar between midnight and 8 A.M.; while Patients 13 and 8, Table 2, on 80 and 30 units respectively, showed a marked fall of the blood sugar between midnight and 8 A.M.

As the peak of activity lies between 6 and 10 hours the necessity of a mid-afternoon feeding is obvious. As significant activity may last over 18 hours, certain patients may also require a bedtime feeding. As the activity is small during the first few hours after injection, a light breakfast should be given. (We have found that a diet distribution of 1/6 carbohydrate at breakfast, 1/3 at lunch, 1/6 at 3 P.M. and 1/3 at dinner, with a bedtime feeding as indicated, gives the most satisfactory results in the majority of patients.) In starting a patient on globin insulin, a fasting blood sugar on two successive mornings, and blood sugar determinations at 3 P.M. and midnight, plus urine sugars to cover postprandial rises will give the most information concerning points of hypoglycemia and the best dietary arrangement.

As shown graphically in Figure 3, globin insulin has more carbohydrate handling ability per unit than protamine zinc insulin. This makes possible the use of one insulin in many patients who had previously been on one injection of regular insulin and one of protamine zinc insulin, either in the same syringe or separately injected.

XUM

TABLE 4.—CLINIC RECORD WITH GLOBIN INSULIN

Name	Globin insulin in units	Previous insulin dose A.M. N. P.M.	No. of months followed	Diet C-P-F[1]	Degree of control[2]
1. R. B. 73 White male No. 518-986	10-20	"New diabetic"	5	200-75-80[a]	Good
2. J. M. 78 White male[6] No. 753-322	15-25	PZI 45	7	150-65-80[a]	Moderately good
3. E. R. 39 White female No. 605-164	20	RI 20-0-0 PZI 30	12	200-75-100[a]	Moderately good
4. L. K. 33 White female No. 314-400	20-25	PZI 35	1	200-75-80[a]	Fair
5. I. T. 30 White male No. 254-813	25-35	"New diabetic"	9	300-90-150[c]	Good
6. C. B. 5 White female No. 744-053	16-24	RI 15-5-5	6	175-70-80[d]	Moderately good
7. G. S. 58 White female No. 39-791	20-28	"New diabetic"	4	200-75-80[d]	Poor to fair
8. R. W. 30 White male No. 134-810	24-30[4]	RI 20-0-20	1	175-60-90[f]	? Fair (infection)
9. M. P. 13 White female No. 772-581	15-40[4]	PZI 20-35-0-0	13	175-90-100[c]	Fair
10. T. H. 13 White male No. 292-338	20-40	CZI 14-18-0-0 PZI 15-25-0-0	6	200-90-95[c]	Moderately good
11. E. L. 30 White female No. 162-277	20-40[3]	RI 10-0-0 PZI 30-0-0	9	100-60-40[f]	Poor to fair
12. C. C. 30 White female[5] No. 265-807	22½-40	RI 10-0-0 PZI 30-0-0	1	250-90-100[b]	Poor[7]
13. H. D. 17 White male No. 798-143	45-50	RI 15-0-20 PZI 0-0-20	1	275-110-120[b]	Good
14. P. K. 16 White Female No. 790-191	80	RI 35-30-30	1	250-100-60[b]	Moderately good
15. N. S. 18 White female No. 420-816	80	CZI 25-0-25 PZI 0-0-35	1	175-70-80[b]	Fair
16. B. B. White female No. 802-266	RI 40 80	RI 80-0-0 PZI 60-0-0	1	?[b]	Poor

KEY TO TABLE 4:

[1] Arrangement of carbohydrate in diet:
- [a] 1/5 breakfast; 2/5 lunch; 2/5 dinner; with or without small bedtime feeding.
- [b] 1/6 breakfast; 1 3 lunch; 1/6 afternoon; 1/3 dinner.
- [c] 1/6 breakfast; 1/3 lunch; 1/6 afternoon; 1/4 dinner; 1/12 bedtime.
- [d] 1/6 breakfast; 1/3 lunch; 1/12 afternoon; 1/3 dinner; 1/12 bedtime.
- [e] ? arrangement, but interval feeding at 3 P.M. and 9 P.M.
- [f] ?

[2] Degree of control graded as % of carbohydrate intake (not including carbohydrate derived from protein) spilled in 24-hour urine:

Good—less than 5% of intake.
Moderately good—less than 10% of intake.
Fair—less than 15% of intake.
Poor—over 20% of intake.

[3] Added 2 to 3 units of regular to globin to decrease burning.

[4] Occasional small doses of regular taken in addition to globin insulin.

[5] Taken off of globin insulin.

[6] Died in hospital 3 months after last clinic visit. Entered in mild acidosis, and died of bronchopneumonia. No details of insulin therapy prior to entry obtained.

[7] Dose ordered cut in half, due to one severe reaction. This is reason for poor control here.

TABLE 5.—TIME OF OCCURRENCE OF INSULIN REACTIONS WITH GLOBIN INSULIN

Time	No. of patients with reactions
8 A.M. to 12 noon	4[2]
12 noon to 3 P.M.	2
3 P.M. to 6 P.M.	6
7 P.M. to 10 P.M.	1
10 P.M. to 12 midnight	2
12 midnight to 5 A.M.	1[3]
5 A.M. to 8 A.M.	1
Time of reaction unknown	2
Reactions	17[1]
No reactions	13

[1] Patients may be listed under 2 to 3 different times of day.

[2] Two of these reactions occurred just before lunch.

[3] Reaction occurred in a patient who was working unusually hard on the "swing shift," at 2 A.M.

While activity may be present between the 18th and 24th hours after injection, in the majority of instances this is very much less than the nocturnal activity of protamine zinc insulin. Eleven of 30 patients had significant activity between midnight and 8 A.M. This point has not been emphasized sufficiently previously. However, only 1 patient had an insulin reaction in this period. This is a point of considerable practical importance in insulin-sensitive patients, frequently children, who have been prone to have reactions between 12 midnight and 8 A.M. with protamine zinc insulin.

The obvious value of the clear solution of globin insulin, obviating mixing of a suspension, as with protamine insulin, is of practical importance to patients. Also in our small series, 36, we have had no local reactions other than burning, and no generalized allergic reactions.

Certain disadvantages are apparent from our studies. Patients who are very insulin-sensitive develop too marked an afternoon hypoglycemia despite interval feeding and a large lunch. From a purely practical viewpoint, a mid-afternoon feeding is not possible for many diabetics who work. Severe diabetics who have large dietary insulin requirements cannot be controlled on one injection of globin insulin due to marked postprandial rises of the blood sugar. Also, diabetics

with high fasting insulin requirements do not receive enough hourly insulin activity at night to prevent rise of the blood sugar at night, even with large doses of globin insulin, as 80 units. One disadvantage not previously mentioned is burning on injection. Two patients complained spontaneously of this, and 7 other patients on questioning stated that globin burned more than regular or protamine zinc insulin. The reason for this is not apparent as the pH is in the same range as regular insulin.

In general, we feel that globin insulin has a place in the treatment of selected diabetics. As with any insulin it is important to understand its activity and duration of effect for most intelligent use.

Summary. *A.* Studies with globin insulin have been made on 36 patients. These included:

1. Eight time-activity curves—doses 10 to 80 units. These showed that the duration varied with the dose and the severity of the diabetes, but in general was 14 to more than 24 hours; average 18 to 19 hours. The peak of activity occurred between the 6th and 10th hours. Onset of activity started within 1 hour of injection but was slow for the first 3 to 5 hours.

2. Comparison of the time-activity function of the same dose of regular, protamine zinc and globin insulin in 2 patients showed that globin insulin was intermediary between regular and protamine zinc insulins as to duration and total carbohydrate-handling ability.

3. Studies with diet—14 patients. The blood sugar curves with diet indicated the necessity for a light breakfast, mid-afternoon feeding, and in some instances a bedtime feeding.

4. Out-Patient Progress records—16 patients (doses 10 to 80 units). The majority of these patients were in fair to good control except for occasional upsets.

B. From these studies we conclude that globin insulin has the following advantages and disadvantages: 1. Advantages: (*a*) In patients controlled with protamine zinc insulin who had severe nocturnal reactions. (*b*) In patients controlled on a combined dose of regular and protamine zinc insulin before breakfast—injected singly or combined. (*c*) More carbohydrate-handling ability than protamine, with earlier peak of action. (*d*) Clear solution, obviating mixing.

2. Disadvantages: (*a*) Too low hourly carbohydrate-handling ability to cover diet in most severe diabetics—doses over 50 units. (*b*) Too short duration of effect to cover nocturnal insulin requirement of severe diabetics. (*c*) Burning on injection in an occasional patient.

Appreciation is expressed to Dr. Solomon Strouse and Dr. Howard West for the use of patients on their services at the Los Angeles County Hospital; and to Burroughs-Wellcome & Company for the supply of globin insulin for investigational use.

REFERENCES

1. Bailey, C. C., and Marble, A.: J. Am. Med. Assn., **118**, 683, 1942.
2. Bauman, L.: Am. J. Med. Sci., **198**, 475, 1939.
3. Duncan, G. G., and Barnes, C. E.: Am. J. Med. Sci., **202**, 553, 1941.
4. Drury, D. R., and Greeley, P. O.: Am. J. Physiol., **127**, 581, 1939.
5. Marks, H. E.: Med. Clin. North America, **24**, 649, 1940.
6. Martin, H. E., and Greeley, P. O.: Arch. Int. Med., **67**, 194, 1941.
7. Martin, H. E., and Greeley, P. O.: Am. J. Med. Sci., **203**, 402, 1942.
8 Martin, H. E., Drury, D. R., and Strouse, S.: Arch. Int. Med., **66**, 78, 1940.

EOSINOPHIL LEUKEMIA

WITH REPORT OF A CASE

BY MARION FRIEDMAN, M.D.
ASSISTANT SURGEON (R)

IRVING J. WOLMAN, M.D.
PASSED ASSISTANT SURGEON (R)

AND

HARLAN H. TYNER, M.D.
ASSISTANT SURGEON (R)
NORFOLK, VA.

(From the U. S. Marine Hospital of the U. S. Public Health Service)

THE existence of eosinophil (eosinophilocytic) leukemia as an entity distinct from myelogenous neutrophil leukemia has not been unequivocally established. A major reason for questioning its separate identity has been the morphologic maturity of eosinophils seen in the peripheral blood and bone marrow of proposed cases, as contrasted with the large numbers of immature and atypical cells found in the more familiar types of leukemia, in "leukemoid" eosinophilic reactions, and in so-called "mixed" leukemia. The issue is complicated also by the well known tendency for eosinophil cells, both mature and immature, to become increased though not dominant in chronic myeloid leukemia.

Eosinophilic leukemia, loosely interpreted, may not be as rare as is suggested by the meager number of instances which have been reported.[1,4,6–10,12,13,15–18] For example, Doan and Reinhart,[3] who analyzed 317 patients with leukemic syndromes, classified 3 as chronic eosinophilic myelogenous leukemia, and described one other having both eosinophilic and basophilic granules within the same malignant myelocytes, as "mixed" chronic myelogenous leukemia. The lack of certainty which attends the diagnostic interpretation of leukemia with eosinophilia prompts this presentation of another case.

Case Report. An 11 year old colored boy was admitted December 17, 1943 to King's Daughters Hospital, Norfolk, Va., with progressive weakness, edema of legs and abdomen, and shortness of breath following an acute eruptive illness a month previously termed "measles." Prior to November, 1942, he was said to have been in good health, though a photograph taken the preceding summer showed him with shoes unlaced, suggesting that swelling of the feet was present even then. He was weak and undernourished and of average height. He had a harsh, moderately productive cough. The nose, cheeks and submaxillary areas were swollen. The upper eyelids were puffy and the eyes lacrimated constantly. The left lacrimal gland was enlarged and palpable. Swollen pale turbinates occluded the nasal passages. The posterior cervical lymph nodes were slightly enlarged, but no other superficial nodes were palpable. Breathing was moderately rapid. Roentgenography showed irregular increased densities throughout the entire lung fields, most prominent at the bases. There was pleural thickening and an enlarged cardiac shadow. Blood pressure was 90/70. The abdomen was not distended but moderate pitting edema of the anterior abdominal wall extended up to the xiphoid. The liver extended two fingers breadth below the costal margin. The spleen could not be felt; there were no palpable abdominal masses. The legs and thighs were

swollen and edematous, the right thigh being larger than the left. Body temperature fluctuated between 36.5° and 38° C. Laboratory studies are shown in Table 2. The patient was kept in bed and given symptomatic treatment. Because of the low blood protein level 500 cc. of blood plasma was administered on December 23, followed by disappearance of the respiratory distress and most of the edema within 72 hours. The thigh circumference, however, continued prominent. He was discharged on January 6 after relief of the immediate symptoms, but rehospitalized from January 19 to January 27 with a recurrence. The pulmonary infiltration was found to have subsided and the cardiac shadow was practically normal in size. No clinical improvement occurred during this admission and the subsequent course at home was progressively downhill.

FIG. 1.—Photograph of the patient taken on March 25, 1943. Note the emaciation of the arms and chest, swelling of the lips, eyelids and salivary areas and open mouth (mouth breathing).

From March 13, 1943, until death on April 17, the patient (Fig. 1) was at the U. S. Marine Hospital, Norfolk, Va. Emaciation, weakness, edema of the lower extremities, rapid respirations, productive cough, swelling of the nose, cheeks, lips and submaxillary areas were prominent features. The submaxillary and sublingual glands were large, hard and discrete. Fine and coarse inspiratory and expiratory râles were audible. The spleen was not felt. The patient had a hearty appetite and consumed large quantities of food. The leukocyte count fluctuated from 126,000 to 194,000 with an eosinophilia from 80 to 94% (Table 1). On March 18 the total blood protein was 5.8 mg. per 100 cc., with 3.4 mg. globulin and 2.4 mg. albumin. Because of this low value, six 250 cc. doses of blood plasma were administered intravenously in a 10-day period, beginning on March 20. During this period the edema subsided, except in the thighs, and the blood protein picture became normal (Table 2): The following laboratory examinations showed results within the normal range; Blood sugar, blood chlorides, blood urea, blood uric acid, blood cholesterol, blood cholesterol esters, icteric index, bleeding time, clotting time, reticulocyte count, platelet count, hematocrit, serologic tests for syphilis, tuberculin patch test, skin test for ecchinococcus, heterophil reaction, fragility test, bromsulphthalein test, and feces for ova and parasites. Two electro-

cardiograms were normal. Roentgen films (Fig. 2) on March 15 revealed rather dense sharply circumscribed shadows throughout both lung fields and enlargement of the heart. Repeat examinations on March 23 and April 6 revealed an increase in these lung field shadows, especially in the lower lobes. Radiography of the skeleton, including the pelvis, showed no abnormalities. The nasal discharge contained eosinophils. Studies of the bone marrow by sternal puncture (Table 3) revealed a predominance of eosinophils with more young forms than in the peripheral blood. On April 16, biopsy of a posterior cervical gland was performed under local anesthesia. The following morning at 3:30 A.M. respirations suddenly ceased.

TABLE 1.—REPRESENTATIVE DIFFERENTIAL CELL COUNT OF PERIPHERAL BLOOD (TOTAL COUNT 126,000) (DONE ON MARCH 25, 1943—500 CELLS COUNTED)

Type of cells	%	
Eosinophils	..	82.0
Promyelocytes	0.0	
Myelocytes	0.4	
Metamyelocytes	0.6	
One-lobed (staff) cells	19.6	
Two-lobed cells	43.0	
Three-lobed cells	15.2	
Four-lobed cells	3.0	
Six-lobed cells	0.2	
Neutrophils	——	4.4
Staff cells	0.4	
Mature cells	4.0	
Basophils	..	0.4
Monocytes	..	4.0
Lymphocytes	..	9.2

Necropsy. The *liver* was large, with yellow-red parenchyma. It weighed 1300 gm. The *spleen* was not enlarged, weighing 90 gm. Its pulp was red, soft and grossly not infiltrated. The small lymph follicles were not unusually abundant. The *kidneys*, *adrenals* and *gastro-intestinal tract* showed no changes. The mesentery was wasted and contained small normal sized *lymph nodes*. A broad chain of enlarged unusually abundant retroperitoneal lymph nodes extended from the pelvis up through the diaphragm, becoming continuous with a mass of large mediastinal nodes in the thorax. Some nodes about the lesser curvature of the stomach and the branches of the celiac axis were similarly enlarged. The average length of these large nodes was 2 to 3 cm. All were soft, discrete and homogeneously gray on section.

A wide sheet of yellow-gray infiltrative tissue, 1 to 2 cm. in thickness, was found in the extraperitoneal fascia of the pelvis, contiguous with the bones but extraperiosteal. This tissue was edematous in areas and not always of the same thickness. Neither bladder nor rectum was invaded. The infiltration continued through the large foramina and beneath the inguinal ligaments down into the soft tissue of both thighs. A great mass of large discrete lymph nodes was found in the right inguinal and femoral region, enveloping the nerves and blood-vessels and extending peripherally along their courses. The upper thigh *muscles* were pale and infiltrated with poorly defined yellow streaks. Similar streaks extended the entire length of the right iliopsoas muscle. The infiltrative changes in the thigh were confined beneath the fascia lata and did not involve the subcutaneous fat. The pleural sacs and the pericardium each contained 100 cc. of clear yellow fluid. The *thymus* was shrunken. The *heart* was dilated and weighed 220 gm. In the posterior mediastinum numerous large lymph nodes extended from the diaphragm to the clavicles and also laterally along the bifurcation of the trachea. The *lungs* were emphysematous and together weighed 360 gm. They contained some gray-red foci of consolidation posterior and inferior to the lower major bronchi. The bronchopulmonary nodes were large and the bronchial walls were thickened. The bronchi were dilated and contained yellow-gray muco-pus. The sphenoid and

TABLE 2.—SIGNIFICANT DATA ON BLOOD STUDIES IN CASE OF EOSINOPHILIC LEUKEMIA

Date:	December				January		March						April	
	17	19	28	29	5	21	15	18	20	22	26	27	31	2	7	13
RBC (in millions)	3.9	..	3.99	3.72	4.65	4.5	5.0	..	5.0	4.5	4.7	..	4.6	5.0	4.9	4.8
Hb. (in gm.)	10.9	..	11.6	11.2	13.0	13.1	13.3	..	15.3	14.0	14.0	..	13.7	..	13.3	14.4
WBC (in thousands)	108	109	162	121	162	135	194	..	169	138	126	..	143	129	170	190
Eosinophils (in %)	81	90	87	85	81	83	92	..	92	90	85	..	89	..	80	88
Neutrophils (in %)	2	2	3	1	0	2	1	..	1	1	5	..	5	..	4	4
Lymphocytes (in %)	17	8	10	14	16	15	7	..	7	9	9	..	6	..	16	8
Monocytes (in %)	0	0	0	0	3	0	0	..	0	0	1	..	0	..	0	0
Platelets (in thousands)	..	..	..	..	..	..	..	..	120	..	150	..	145	..	..	155
Total proteins (in gm. %)	5.36	..	..	..	..	..	..	5.8	..	6.7	..	6.5	7.5	7.6	7.4	6.8
Albumin (in gm. %)	2.18	..	..	..	..	..	..	2.4	..	3.9	..	3.4	4.4	4.0	3.7	3.5
Globulin (in gm. %)	3.18	..	..	..	..	..	..	3.4	..	2.8	..	3.1	3.1	3.6	3.7	3.3
A/G ratio (in gm. %)	0.68	..	..	..	..	..	..	0.7	..	1.4	..	1.1	1.4	1.1	1.0	1.1

ethmoid *sinuses* were filled with green muco-pus. Their lining mucous membrane was thickened, polypoid and discolored. The *bones* had normal external contours and red succulent marrow.

Microscopy. *Lungs.* The hilar connective tissue was thickened and edematous. The bronchi were abnormally large, with hyperplastic mucous membrane. They contained exudate and the bronchiolar epithelium was rich in eosinophils. The mucous and submucous coats and the supporting tissue of the bronchial glands, as well as the peribronchial fascia and bronchioles, were infiltrated with a mixture of mature eosinophils and faintly basophilic cells having irregular pale staining cytoplasm and large rounded or indented vesicular muclei. These took the oxidase stain and were judged to be eosinophilic myelocytes. Adult neutrophils and lymphocytes were infrequent. The pulmonary capillaries were distended, some being filled with leukocytes, chiefly eosinophils. Many alveoli were filled with an acute pneumonic exudate, with nearly all the invading cells being mature eosinophils. In other alveoli the walls were thickened and the lumens contracted with organizing tissue occupying the lumens. Eosinophils were abundantly present within their walls.

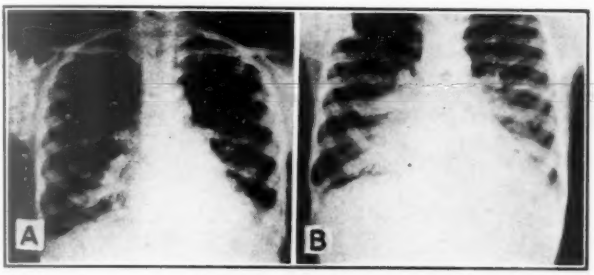


FIG. 2.—Roentgenograms of chest showing progressive involvement of hilar regions and lower lobes by eosinophilic infiltration, verified by necropsy. *A*, January 21, 1943; *B*, April 6, 1943. Note enlargement of the heart shadow. (Photographs by Dr. Robert Drelich, U. S. Marine Hospital, Norfolk, Va.)

TABLE 3.—DIFFERENTIAL CELL COUNTS OF ASPIRATED BONE MARROW (500 CELLS COUNTED)

Type of cells	% Dec. 20, 1942	Mar. 19, 1943
Myeloblasts	0.8	0.4
Eosinophilic series	65.0	74.2
Promyelocytes A	3.2	1.4
Promyelocytes S	4.9	4.2
Myelocytes	14.0	9.0
Metamyelocytes	9.1	6.4
One-lobed (staff) cells	6.6	12.8
Two-lobed cells	15.1	25.6
Three-lobed cells	9.8	13.6
Four-lobed cells	2.3	1.2
Neutrophilic series	13.0	9.4
Myelocytes	1.0	0.0
Metamyelocytes	1.9	0.0
Staff cells	4.0	2.6
Polymorphonuclears	6.1	6.8
Basophilic myelocytes	—	0.4 — 0.4
Lymphocytes	10.4	12.2
Monocytes	0.2	0.6
Red cell series	10.2	2.8
Megaloblasts	2.8	1.2
Pronormoblasts	3.7	0.8
Normoblasts	3.7	0.8

Lymph Nodes. The germ centers were hyperplastic and the lymph sinuses filled with lymphocytes. Eosinophils were present in very small numbers inside the node, though infiltrating heavily the pericapsular fascia.

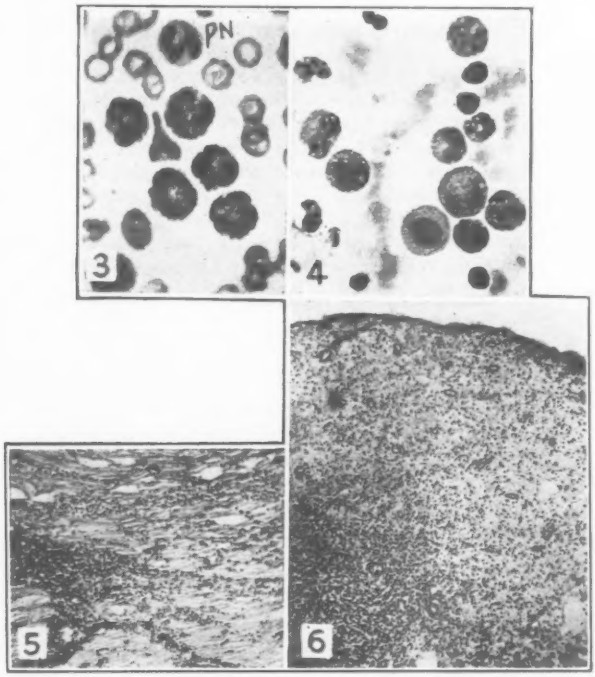


FIG. 3.—Photomicrograph (× 1000) of a typical peripheral blood smear, showing the esentially normal mature appearance of the eosinophils in the circulation. A polymorphonuclear neutrophil is included, demonstrating that the eosinophils are not unusually large.

FIG. 4.—Photomicrograph (× 1000) of bone marrow aspirated December 20, 1942. The larger leukocytes are eosinophil myelocytes, with granular cytoplasm and oval or indefinite nuclei. The nucleus of one cell is hyperchromatic. The smaller leukocytes are more mature forms having "staff" rod-shaped nuclei. Several lymphocytes, one polymorphonuclear neutrophil and one normoblast are also shown.

FIG. 5.—Photomicrograph (× 100) of striated muscle showing leukemic infiltration of the tissue, most marked in the interfascicular fascia.

FIG. 6.—Photomicrograph (× 100) of hypertrophied mucous membrane of sphenoid sinus. There is heavy infiltration of the interstices with leukemic cells. Study under higher power shows that many of the eosinophils present are immature and apparently proliferating *in situ*.

Pelvic Fascia. The connective tissue layers were broadened, having a loose mucinoid stroma containing great numbers of infiltrating cells homogeneously distributed. About two-thirds of these cells were mature or nearly mature eosinophils. The majority of the remaining cells were larger, with round or oval nuclei of coarse chromatin structure and a relatively large amount of oxidase-positive basophilic non-granular cytoplasm. The adult eosinophils took the fat stain in frozen sections whereas those less mature did not.

Liver. The individual hepatic cells were hypertrophied with refractile granular cytoplasm. Many eosinophils lay within the sinusoidal spaces and the connective tissue.

Spleen. The Malpighian follicles were small and not numerous; their centers were not hyperplastic. The leukocytic elements of the pulp appeared

somewhat increased. Large numbers of eosinophils were scattered through the sinuses and pulp spaces, most abundant about the periphery of the lymph follicles. The majority of the eosinophils were mature cells, though occasional ones were myelocytes or metamyelocytes.

Bone Marrow. Ribs, vertebræ, sternum, pelvis and skull were identical, with highly cellular marrow spaces and uninvolved trabeculæ. The great majority of the myeloid cells were eosinophils with morphology and age distribution essentially the same as in the aspiration counts given in Table 3. Other cells with agranular cytoplasm were present in moderate numbers, uniformly mixed (Fig. 4).

Ilio-psoas and Thigh Muscles. Many muscle bundles were penetrated or compressed by infiltrating areolar tissue. The cells in this invading tissue consisted of eosinophilic granule-containing cells and younger presumably immature eosinophils (Fig. 5).

Sphenoid Sinus. The mucous membrane was thrown up in hyperplastic folds 5 to 20 times thicker than normal. The mucous membrane matrix was composed of loose areolar mucinoid connective tissue, rich in young thin-walled capillaries and heavily infiltrated with eosinophilic leukocytes of all ages. Neutrophils and lymphocytes were uncommon. The sinus contents consisted largely of mucus, infiltrated with degenerated unidentifiable leukocytes (Fig. 6).

Gastro-intestinal Tract. Eosinophils of various ages had densely infiltrated all layers of the stomach, the submucous and muscular coats being several times normal thickness. No changes were noted in the intestine apart from sporadic eosinophils. These cells were abundant also in the retroduodenal fascia.

Diaphragm. The subserosal connective tissue on each aspect and many of the interfascicular layers were infiltrated with eosinophilic cells.

Right Femoral Nerve. Fibers and sheaths were intact, but the enveloping fascia were heavily infiltrated.

PATHOLOGIC DIAGNOSIS. Chronic eosinophilic leukemia, with eosinophilic infiltration of bone marrow, thighs, back muscles, stomach, salivary glands, pelvis, lymph nodes, lungs, nasal mucous membranes, femoral nerve, and other tissues; enlargement of the liver; chronic sinusitis; chronic pneumonia and bronchiectasis; emaciation.

Discussion.—This boy was judged to have had chronic myelogenous leukemia, eosinophilic variety, inasmuch as he showed the major nosologic manifestations of leukemia agreed upon by current authoritative opinion.[5,11,14,19,20] He suffered from weakness, cachexia and loss of weight progressing to a fatal outcome; the leukocyte count was extremely high (126,000 to 194,000 cells per c.mm.); 80 to 92% of the white cells in the circulation were eosinophils, nearly all mature, to be sure, though occasional young or abnormal forms were demonstrable; the bone marrow, lymph nodes, pelvic fascia, thigh and back muscles, salivary glands, lungs, stomach, nasal mucous membrane and other tissues were infiltrated with myeloid accumulations of eosinophils. None of the other disorders which may give rise to high eosinophilia were known to be present in this patient. An interesting clinical phenomenon was the presence on two occasions of hypoproteinemia with dependent edema, probably secondary to dysfunction of the enlarged liver, and prompt relief of these symptoms by intravenous administration of blood plasma. That such other findings as splenomegaly, marked anemia, architectural destruction of spleen and lymph nodes, hemorrhages, and thrombocytopenia were absent does not seem of sufficient significance to invalidate the diagnosis; these features are

TABLE 4.—REPORTED CASES OF EOSINOPHILIC LEUKEMIA

Author	Age when first seen	Duration of symptoms	Range of WBC	Range of eosinophil (%)	Type of eosinophil in peripheral blood	Organs macroscopically affected
			Acute Cases			
Hay and Evans, Case 1 (1929)	41	Less than 3 wks.	72,187 (terminal)	83.7 (terminal)	Mature	Lymph glands, spleen
McCowan and Parker (1932)	45	13 days (?)	154,000–20,000	78.5–?	29.5% myelocytes	Spleen
Stephens (1935)	17	2–3 mos.	130,000 (only figures noted)	68.6	1% metamyelocytes	Lymph glands, lungs
Forkner *et al.* (1937)	33	27 days	265,500–118,000	82.0–75.0	Many myeloblasts; only 27% mature	Lymph glands, spleen, liver, lungs
			Chronic Cases			
Giffin (1919)	31	7½ yrs.	211,000–15,400	90.7–66.3	Mature	Lymph glands, liver, spleen, heart
Shapiro (1919)	48	6 yrs.	236,000–15,700	90.0–48.5	0.6–5% myelocytes	Lymph glands, liver, spleen, lungs
McDonald and Shaw (1922)	46	8 yrs. (alive when reported)	138,250–34,000	82.0–71.4	Mature	Lymph glands, spleen
Harrison (1930)	23	23 mos.	16,000–13,450	60.0–30.0	Mature	Lymph glands, spleen, liver, lungs
Drennan and Biggart (1930)	15	16 mos.	73,170–32,760	70.0–23.0	Mature	Lymph glands, spleen, liver, lungs, left leg
Thomsen and Plum (1939)	11	13 mos.	65,000–3,900*	90.0–0*	62% mature; after irradiation, 81% myeloblasts	Lymph glands, spleen, liver, heart
Goehl (1942)	18	10 mos.	190,900–7,800	88.0–5.0	Mature	Lymph glands, spleen
			Unclassified Case			
Stillman (1912)	27	No mention (alive when reported)	165,000–118,000	91.4–85.8	20% metamyelocytes, 2% myelocytes	Lymph glands, spleen, liver
			Mixed Cases			
Alexander (1924)	50	9 yrs.	150,200–16,800	36.0–21.5	Mature	Spleen, liver, lungs, heart
Hay and Evans, Case 2 (1929)	53	2¾ yrs.	62,180–16,000	55.0–16.1	Mature	Spleen, liver, heart, kidneys

* Due to irradiation.

XUM

not universal in any variety of human leukemia. Even though observed symptoms dated back but 5 months, the absence of anemia, the persistence of the platelets at or near a normal level, and the failure of the marrow to show infiltration with primitive blast forms, suggest that this case be classed as chronic or subacute, rather than as acute, leukemia.

A survey of 12 somewhat similar cases that have been reported as eosinophil leukemia, along with the instance here reported, brings out certain significant features (Table 4). Twelve were males. The ages ranged from 11 to 48 years, though 5 were under 20 when symptoms began. Four cases were acute, 8 chronic including the present case, and 1 unclassified. Weakness was complained of by 7, prostration by 3 and gastro-intestinal disturbances by 5. Lymph node enlargement was noted in 10, with 2 others displaying this at necropsy. Ten had splenomegaly clinically and this was found at necropsy in 1 additional case. Hepatomegaly was present in 8, and hemorrhagic manifestations in 5. Five were edematous. Fever was not encountered. Attempts at therapy consisted of irradiation in 1 case, small doses of Fowler's solution in 1, splenic extract in 1, and 2 splenectomies. Irradiation and Fowler's solution caused marked decrease in the leukocytosis. Splenectomy was followed by increase in the number of leukocytes though with some clinical improvement. Death was usually from exhaustion.

As for the blood, 10 out of 12 cases showed anemia during some portion of the disease, usually terminally, though the anemia was severe only in 2. Platelet counts were performed in 2 of the acute cases, one value being 69,000 per c.mm.,[10] the other less than 5000.[6] In the 4 cases of chronic leukemia where recorded the values ranged from 140,000 to 360,000. The total white count was nearly always high, every case except one[9] (16,000) having been at one time or another between 65,000 and 312,000 per c.mm.; no instances of transient depression of the total count with an interval phase of aleukemic leukemia were encountered. The mature eosinophils were as a rule typical, with segmented nuclei and densely refractile granules. Several authors commented that the adult cells seemed unusually large, but this distinction must be made with care since the diameter of leukocytes in blood films depends to great extent on the thickness of the smear. Vacuoles in the cytoplasm and granules of irregular size and abundance have been described. In the patient here reported, the adult eosinophils were of normal appearance, but in the myelocytes and metamyelocytes the quantity and maturity of the eosinophilic granulations were not always in the same stage of maturity as were the nuclei. Thus, for example, cells having the nearly mature rod-like nucleus of the staff cell type often contained but few immature eosinophilic and basophilic granules, grouped in one portion of the basophilic cytoplasm. The most common hematologic change has been the migration of immature cell forms—myelocytes, metamyelocytes and stab cells—into the blood stream. Infrequently, these have been numerous, up to 73% of the total eosinophils on one count in Forkner's patient. In

XUM

another unusual case[18] 80% of the circulating leukocytes were judged to be primitive myeloblast forms. In several other instances immature cells represented 0.5 to 5% of the differential count. However, in fully half of the cases no immature cells were seen in the circulating blood.

Pathologically, organ infiltration by proliferating eosinophilic myeloid tissue was noted in lymph nodes and spleen in 9 cases, in kidneys 4 times, and invariably in the bone marrow when studied. Pulmonary infiltrations were observed in 6 instances; the Roentgen appearance of these resembled tuberculosis or chronic lung infections. The present patient had heavy invasion of many body structures by eosinophils but a negligible degree of infiltration into the spleen. One other patient in addition to ours—Drennan and Biggart's[4] 15 year old boy—showed a pelvic mass and involvement of the psoas and leg musculature. Myocardial dilatation with formation of antemortem thrombi within the heart was noted 4 times; Shapiro's[15] case had leukemic infiltration of the heart muscle and Giffin's[7] showed chronic obliterative pericarditis. In the case here reported many eosinophils were present in the alveolar exudate of chronic pneumonia, in the mucopurulent secretion of bronchiectasis and sinusitis, and in the thickened mucous membrane of obstructed nasal accessory sinuses. The appearance of the exudate suggested that the eosinophils in these areas were actively participating as phagocytic agents of chronic inflammation.

The eosinophil is known to be a type of cell which proliferates readily in the presence of a wide diversity of constitutional disorders. Hence it is unexpected to find this cell more resistant to the inciting agent of leukemia, whatever that may be, than nearly every other kind of leukocyte in the circulation, as attested by the great paucity of such cases on record. Consequently, every patient with prolonged persistent eosinophilia suspected of having leukemia should receive exhaustive study to rule out other known causes of this blood reaction. Even eosinophilic myeloid hyperplasia or infiltration of eosinophils into biopsied lymph nodes are not in themselves pathognomonic signs of leukemia, for, as Bass[2] experienced, these findings can persist for months in chronic eosinophilia, and then later fade away. Indeed medical progress may disclose some day that clinical pictures of the type discussed here have an infectious rather than a neoplastic origin, and should be classed among the inflammations rather than as leukemia.

Summary.—A case of leukemia in an 11 year old colored male is presented. Clinically there was weakness, emaciation, chronic cough, generalized enlargement of the lymph nodes of the head and neck, hepatomegaly, dependent edema, leukocytosis up to 194,000 cells per c.mm., eosinophilia ranging from 80 to 90% with nearly all mature cells, and decrease in total proteins with inversion of the albumin/globulin ratio. Necropsy demonstrated increase of mature and immature eosinophils in the bone marrow, with infiltration into lymph nodes, pelvic fascia, thigh and back muscles, salivary glands, lungs, stomach, nasal mucous membrane and other tissues. The spleen was but slightly involved. This instance and 12 others found in the hematologic

literature seem to be best characterized as manifestations of leukemic overgrowth of the eosinophil blood cells, though admittedly the nosologic basis for this interpretation rests solely on morphologic evidence.

REFERENCES

1. Alexander, M. E.: J. Lab. and Clin. Med., **9**, 803, 1924.
2. Bass, M. H.: Am. J. Dis. Child., **62**, 68, 1941.
3. Doan, C. A., and Reinhart, H. L.: Am. J. Clin. Path., **11**, 1, 1941.
4. Drennan, A. M., and Biggart, J. H.: J. Path. and Bact., **33**, 995, 1930.
5. Forkner, C. E.: Leukemia and Allied Disorders, New York, Macmillan, 1938.
6. Forkner, C. E., Leng, C. T., Chu, Y. C., and Cochran, W.: Chinese Med. J., 51, 609, 1937.
7. Giffin, H. Z.: Am. J. Med. Sci., **158**, 618, 1919.
8. Goehl, R. O.: Lancet, **62**, 252, 1942.
9. Harrison, F. F.: Am. J. Med. Sci., **179**, 208, 1930.
10. Hay, J., and Evans, W. H.: Quart. J. Med., **22**, 167, 1929.
11. Kracke, R. R.: Diseases of the Blood, 2nd ed., Philadelphia, Lippincott, 1941.
12. McCowan, G. R., and Parker, H. B.: J. Roy. Nav. Med. Serv., **18**, 131, 1932.
13. McDonald, S., and Shaw, A. F. D.: Brit. Med. J., **2**, 966, 1922.
14. Osgood, E. E.: Atlas of Hematology, San Francisco, Stacey, 1937.
15. Shapiro, L. G.: Proc. Path. Soc. New York, **19**, 73, 1919.
16. Stephens, D. J.: Am. J. Med. Sci., **189**, 387, 1935.
17. Stillman, R. G.: Med. Rec., **81**, 594, 1912.
18. Thomsen, S., and Plum, P.: Acta med. Scandinav., **101**, 116, 1939.
19. Whitby, L. E. H., and Britten, C. J. C.: Disorders of the Blood, 4th ed., London, Churchill, 1942.
20. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942.

PLASMA LIPIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING GOLD SALT THERAPY AND DURING PREGNANCY

By Theodore B. Bayles, M.D.*

RESEARCH FELLOW, ROBERT BRECK BRIGHAM HOSPITAL; JUNIOR ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL

AND

Charlotte B. Riddell

RESEARCH TECHNICIAN, ROBERT BRECK BRIGHAM HOSPITAL

BOSTON, MASS.

(From the Medical Service, Robert Breck Brigham Hospital)

Rheumatoid arthritis has been studied from innumerable points of view and recently certain pathologic and physiologic states which greatly modify this disease have been clarified. Jaundice and pregnancy are the outstanding conditions which cause, in most instances, an about face in the course of this disease. Hench[16,17] has reviewed the historical background of the effect of both these factors and presented a clinical analysis of 16 patients with rheumatoid arthritis who have become pregnant during their disease. Fifteen of these "experienced striking, generally complete, relief during pregnancy and for variable periods thereafter." Eleven patients with rheumatoid arthritis who became pregnant have been studied at this hospital.[1] Ten of these noted marked relief of pain and diminution in swelling during the pregnancy. As in Hench's group, most of our patients noticed the ameliorative effect before the 3rd month and this continued until

* On leave of absence.

at least 1 month after delivery and usually longer. Others have made the same observations in scattered cases of pregnancy in rheumatoid arthritics. Two important additions to the problem of study and treatment of rheumatoid arthritis stem from these observations. First, the course of rheumatoid arthritis can be dramatically altered and apparently temporarily reversed by changes in the total metabolism of the body brought about by such pathologic or physiologic states as jaundice and pregnancy; second, nature has provided a signpost which points to a new direction for the investigation of this disease.

Pregnancy produces protean physiologic changes which might be studied in patients with rheumatoid arthritis. We have observed the lack of therapeutic response in female arthritic patients receiving massive doses of the best known hormones of pregnancy (estrogens, progestins and chorionic gonadotropin) administered singly and together.[2] A review of the physiologic changes in pregnancy that might be the cause of the ameliorative effect revealed that one of the most profound chemical changes was that of a great increase in plasma lipids.[5,21,23] In view of the lipemia of obstructive jaundice,[8,9,10,24,25] this fact seemed peculiarly interesting.

The lipemia of pregnancy is due almost entirely to an increase in plasma lipids, the red cells showing but little change. The neutral fat of the plasma begins to increase in the first trimester, while phospholipid and cholesterol rise in the second trimester. At term phospholipid and free cholesterol are each increased 25% and neutral fat over 100% over their value in non-pregnant women. The lipemia revealed no shift in lipid ratios and the iodine numbers of the fatty acids involved indicate no change in their composition; while in birds estrogenic substances have been shown to increase the blood lipid levels,[7] and Corwin[12] has been able to produce a sustained hyperlipemia in dogs by feeding phospholipids. Attempts to produce lipemia in humans have been unsuccessful and the actual cause of lipemia in pregnancy is yet to be disclosed. Boyd[5] lists 15 causes for the lipemia of pregnancy, none of which is proven by experimental data. Likewise the increase in blood lipids in obstructive jaundice, untreated diabetes mellitus and severe anemia is unexplained.

Freyberg and his associates[3] have published a study in which they compared the partitioned plasma lipids in obstructive jaundice and in patients with rheumatoid arthritis to determine if the increase in serum lipids in the former condition could account for the beneficial effect of jaundice in rheumatoid arthritis. They confirmed previous studies[13,18,19] that total serum lipids and its fractions are normal in patients with rheumatoid arthritis and concluded that jaundice is not beneficial to arthritic patients by reason of correcting a lipid deficiency, but it is possible that the extremely high levels of total lipids, phospholipids and total and free cholesterol which are present in jaundice may be a factor in causing the beneficial effect of jaundice on arthritis. These workers did not confirm the work of Bruger *et al.*[14,15] who reported a decrease in total cholesterol with a normal ratio of free cholesterol to cholesterol ester.

In order to extend these studies and determine if there was any peculiarity in the lipemia of pregnant arthritics as compared to normal pregnancy, we have studied 3 groups of patients with active rheumatoid arthritis: (*a*) those receiving standard non-specific therapy; (*b*) those receiving the former with added gold salt therapy; and (*c*) arthritics during pregnancy and after delivery. The patients receiving gold salt therapy (Group *b*) were included to see if this form of treatment, thought by some workers to be helpful, shifted the plasma lipids in any way.

Procedure. Plasma lipid studies were made on 21 patients with active rheumatoid arthritis as manifested by painful swelling of the joints, anemia, weight loss and increased erythrocyte sedimentation rate, 10 of whom (Group *a*) received non-specific treatment and 11 the same régime with added gold salt therapy (Group *b*). In the latter group serial observations were made in the course of treatment—usually at the beginning, halfway through (after administration of approximately 500 mg. of the gold salt), and at the end of treatment (after 1000 mg. of gold salt). In the presence of no specific blood dyscrasia, with normal urinary findings, and in the absence of a history of kidney or liver disease, or of a sensitivity to drugs, these patients received one 25 mg. dose, one 50 mg. dose and 19 weekly doses of 100 mg. each of a soluble intramuscular preparation (gold content, 50%). This gave a total of 1975 mg. over a period of 21 weeks. All the patients were hospitalized for this therapy.

Four pregnant rheumatoid arthritics (Group *c*) were studied, 3 prepartum and postpartum and 1 during pregnancy. All 4 had activity at the time of conception and enjoyed freedom from arthritic symptoms from 3 months pregnant to a month or more after delivery.

All blood samples were taken after a 15-hour fasting period. The diets of the few out-patients studied were all normal and the remainder (over 90%) had been on the standard house diet of the Robert Breck Brigham Hospital for days or weeks before the sample was taken. Clinical and laboratory studies ruled out hypothyroid, diabetic, nephritic and hemorrhagic lipemia.

Chemical Methods. According to the method of Bloor,[4] a filtrate of an alcohol ether extract was prepared from 2 cc. of plasma. Aliquots of this filtrate were used for the determination of various lipid fractions. Total lipid and cholesterol were obtained by the sulfuric acid-dichromate oxidation method. Phospholipid phosphorus was determined in duplicate by an unpublished modification of the Fiske-Subbarow aminonaphthol-sulfonic acid-phosphate method adapted to the Klett photoelectric colorimeter.[11] The cholesterol ester value was determined by calculation using 68% of total cholesterol, since in normals,[20,22] rheumatoid arthritics[3,13,14,15,18,19] and pregnant women[5,21] this figure has been found to obtain. Total fatty acids, total phospholipid, phospholipid fatty acid, cholesterol ester fatty acid, neutral fatty acid, neutral fat and the lipid ratios were calculated.[6]

Results and Comments. Table 1 gives the results of the analyses done on a series of rheumatoid arthritic patients receiving non-specific treatment (Group *a*), and on a second series receiving gold salt therapy (Group *b*). The total lipid values in the patients without gold salt therapy (Group *a*) and in the Group *b* patients before gold salt therapy varied from 306 to 611 mg. per 100 cc. of plasma. Plasma total cholesterol varied from 110 to 217 mg. per 100 cc., averaging 151; the phospholipid range was from 169 to 250. These figures and the other calculated lipid constituents and ratios are within the well-established limits for normal subjects and for patients with rheumatoid arthritis.[3,13,18,19]

TABLE 1.—PLASMA LIPIDS IN RHEUMATOID ARTHRITICS DURING GOLD SALT THERAPY (RESULTS IN MG. PER 100 CC. OF PLASMA)

Subject	Age (yrs.)	Sex	Duration of disease (mos.)	Total lipid	Total fatty acid	Phospholipid fatty acid	Cholesterol ester fatty acid	Neutral fatty acid	Neutral fat	Cholesterol		Phospholipid phosphorus	Phospholipid	Total lipid/Total fatty acid	Total fatty acid/Neutral fat	Total fatty acid/Phospholipid	Phospholipid/Total cholesterol
										Total	Ester						
						Patients With Rheumatoid Arthritis (Group a)											
1	54	M	4	414	260	135	62	63	60	135	92	8.25	203	1.59	4.34	1.28	1.50
2	62	F	7	460	299	141	72	86	82	158	107	8.45	211	1.54	3.64	1.41	1.32
3	33	M	12	537	394	121	66	107	101	145	99	7.29	182	1.36	3.90	2.16	1.25
4	41	M	12	348	207	130	64	13	12	139	95	7.80	195	1.68	17.20	1.06	1.40
5	24	M	30	398	243	136	85	22	21	187	127	8.18	205	1.64	11.50	1.18	1.10
6	33	M	36	463	309	143	70	96	91	153	104	8.55	214	1.50	3.4	1.44	1.40
7	43	F	84	352	212	154	62	..	..	137	93	9.20	230	1.66	..	0.92	1.67
8	56	F	96	611	408	148	92	168	159	202	137	8.93	223	1.50	2.56	1.82	1.10
9	40	M	120	306	196	130	50	16	15	110	75	7.80	195	1.56	13.00	1.00	1.77
10	38	F	228	416	283	134	60	87	83	132	90	8.05	201	1.47	3.40	1.41	1.52
						Patients During Gold Salt Therapy (Group b)											
1	54	M	6	430	318	133	52	133	126	113	77	8.00	200	1.35	2.52	1.59	1.77
				375	258	132	53	73	70	116	79	7.96	199	1.45	3.69	1.29	1.71
				398	252	127	65	60	57	143	97	7.60	190	1.58	4.40	1.32	1.32
2	19	F	7	458	310	158	66	86	82	146	99	9.53	238	1.47	3.60	1.30	1.63
				420	296	158	57	81	77	125	85	9.50	238	1.42	3.60	1.24	1.90
				380	310	129	58	123	118	128	87	7.75	194	1.22	2.50	1.60	1.51
3	54	M	10	481	370	140	52	178	169	114	78	8.43	211	1.30	2.19	1.75	1.85
				460	350	141	51	158	150	113	77	8.50	212	1.31	2.33	1.65	1.86
				478	319	159	72	88	84	157	107	9.50	238	1.49	3.80	1.34	1.51
4	25	M	12	—	—	—	—	—	—	—	—	—	—	—	—	—	—
				409	285	149	56	80	76	124	84	8.97	224	1.43	3.61	1.27	1.81
				452	319	134	60	125	119	132	90	8.10	202	1.42	2.68	1.58	1.53
5	18	F	15	489	346	160	65	121	115	142	97	9.68	241	1.41	3.00	1.43	1.70
				420	310	155	50	105	99	110	75	9.31	233	1.35	3.12	1.32	2.12
				433	290	158	67	65	62	147	100	9.54	238	1.49	4.68	1.22	1.62
6	28	F	18	408	201	157	92	48	..	202	137	9.41	235	2.03	..	0.86	1.16
				594	346	193	110	43	41	243	165	11.60	290	1.71	8.44	1.19	1.19
				548	301	172	109	33	31	240	163	9.55	239	1.82	9.72	1.25	1.00
7	15	F	20	433	270	132	72	66	63	158	107	7.91	198	1.60	4.29	1.36	1.25
				424	320	141	48	131	124	194	71	8.50	212	1.32	2.58	1.51	2.20
8	50	M	24	415	295	145	55	95	90	120	82	8.70	218	1.40	3.28	1.35	1.81
				567	325	166	99	60	57	217	147	10.00	250	1.74	5.70	1.30	1.15
				684	450	192	105	153	145	229	156	11.50	288	1.52			

6	28	F	18	408	201	157	92	48	..	202	137	9.41	235	2.03	..	0.86	1.16
				594	346	193	110	43	41	243	165	11.60	290	1.71	8.44	1.19	1.19
				548	301	172	109	33	31	240	163	9.55	239	1.82	9.72	1.25	1.00
7	15	F	20	433	270	132	72	66	63	158	107	7.91	198	1.60	4.29	1.36	1.25
				424	320	141	48	131	124	104	71	8.50	212	1.32	2.58	1.51	2.20
8	50	M	24	415	295	145	55	95	90	120	82	8.70	218	1.40	3.28	1.35	1.81
				567	325	166	99	60	57	217	147	10.00	250	1.74	5.70	1.30	1.15
				684	450	192	105	153	145	229	156	11.50	289	1.52	3.10	1.55	1.26
9	20	F	36	660	443	179	98	166	157	215	146	10.70	269	1.49	2.82	1.64	1.25
				412	270	150	64	56	53	140	95	9.02	225	1.52	5.10	1.20	1.60
				430	266	154	74	38	36	162	110	9.27	232	1.61	7.40	1.15	1.42
10	20	F	48	502	300	152	90	58	55	197	137	9.15	229	1.67	5.40	1.31	1.16
				379	203	149	78	24	..	171	116	9.00	225	1.87	..	0.90	1.31
				391	246	139	58	49	47	128	87	8.37	209	1.59	5.23	1.18	1.62
				457	310	132	66	112	106	145	99	7.95	199	1.47	2.92	1.56	1.37
11	24	F	48	395	245	112	66	67	64	146	99	6.76	169	1.61	3.90	1.45	1.15
				419	273	121	62	90	86	135	92	7.36	184	1.52	3.20	1.48	1.36
				407	297	133	51	113	107	112	76	7.95	199	1.37	2.80	1.49	1.78

TABLE 2.—PLASMA LIPIDS IN RHEUMATOID ARTHRITICS DURING PREGNANCY (RESULTS IN MG. PER 100 CC. OF PLASMA)

Subject	Age (yrs.)	Duration of arthritis (mos.)	Stage of gestation (wks.)	Total lipid	Total fatty acid	Phospholipid fatty acid	Cholesterol ester fatty acid	Neutral fatty acid	Neutral fat	Cholesterol		Phospholipid phosphorus	Phospholipid	Total lipid/ Total fatty acid	Total fatty acid/ Neutral fat	Total fatty acid/ Phospholipid	Phospholipid/ Total cholesterol
										Total	Ester						
Patients With Rheumatoid Arthritis During Pregnancy (Group c)																	
1	33	24	12	426	306	121	56	129	122	122	83	7.30	182	1.39	2.50	1.68	1.49
			28	550	425	167	58	200	190	128	87	10.05	251	1.29	2.24	1.69	1.96
			6*	365	249	156	60	33	31	116	79	9.40	235	1.46	8.05	1.06	2.02
2	35	60	28	613	397	172	97	128	122	213	145	10.35	259	1.54	3.25	1.53	1.21
			12*	486	333	148	69	116	110	151	103	8.92	223	1.46	3.03	1.49	1.47
3	28	28	32	604	412	165	87	160	152	192	136	9.15	248	1.47	2.70	1.66	1.29
			16*	425	293	113	60	120	114	131	89	6.80	170	1.45	1.92	1.72	1.30
4	39	48	16	389	273	148	54	71	67	117	80	8.90	222	1.42	4.08	1.23	1.90
			32	519	397	164	57	176	167	125	85	9.90	247	1.30	2.38	1.60	1.97

* Postpartum.

Gold salt therapy had startlingly little effect on partitioned plasma lipids, as shown in Table 1. Total lipids increased in 6 patients an average of 76 mg. per cc. and decreased in 5 an average of 35. Total cholesterol increased in 6 an average of 30 mg. per cc. and decreased in 5 an average of 23. Phospholipid values increased an average of 17 mg. per cc. in 6 patients and decreased an average of 21 in 5 patients. Calculated lipid constituents and ratios were unaltered during gold salt therapy. Apparent or real clinical improvement in patients during gold salt therapy was not correlated in any way with the individual plasma lipid changes noted in Table 1. It is not the purpose of this paper either to defend or abuse gold salt therapy in rheumatoid arthritis; but if it is a useful medicament in this disease, it can be seen from our results that the ameliorative effect is not brought about by a significant shift in the plasma lipids.

The changes in plasma lipids in rheumatoid arthritics during pregnancy (Group *c*) are shown in Table 2. Total lipids in 28 to 32 weeks of pregnancy had increased 26, 33, 42 and 50% in our cases. Schwarz *et al.*[21] have found a variation of from 34 to 122% increase of total lipids at term, in their study of the development of lipemia during pregnancy, and point out in their paper that this increase is progressive and at a relatively constant rate. This would indicate that at term the total lipids in our patients would be within the range of the lipemia of pregnancy in normal subjects. The total cholesterol increase was 7, 10, 41 and 46% in our patients. This can be compared with Schwarz *et al.* who found a variation of 8 to 136% increase at term, and Boyd[5] who reports a 25% average increase. These data indicate no unusual shift in total cholesterol in the pregnant arthritic. In our patients the phospholipid change was +7, 11, 16 and 45%, compared with Schwarz *et al.* who found a range of 20 to 160% increase at term, and Boyd's figure was a 25% average rise for this substance at term. Thus, the phospholipid shift was not unusual by actual measurement in pregnant rheumatoid arthritics. The calculated lipid substances and ratios shown in Table 2 show no unusual changes during pregnancy in rheumatoid arthritis as compared to those found during pregnancy in a normal subject.[5,21,23]

While the ameliorative effect of pregnancy on rheumatoid arthritis is nearly as great as that of obstructive jaundice, it can be seen from our figures and those of others that the total lipid increases during pregnancy are minimal as compared to the profound lipid disturbance in obstructive jaundice.[3,8,9,10,24,25] In this latter condition Freyberg[3] found the total serum lipids are increased about 300%. The total cholesterol increased approximately 75%, with free cholesterol rising 3 to 4 times normal and the ester value remaining relatively unchanged. Phospholipids increased 200%.

If we compare these figures with those in the lipemia of pregnancy, the total cholesterol rise is seen to be only one-third that of jaundice with no change in the free/ester ratio. In this respect it differs greatly from the lipemia of jaundice, in which the hypercholesterolemia is almost entirely due to a great increase in free cholesterol with the esters

either remaining unchanged or below normal. Since the ameliorative effect of jaundice and pregnancy on rheumatoid arthritis is qualitatively the same, the difference in cholesterol metabolism in these two conditions cannot be invoked as the answer to the problem, and is probably unrelated to the favorable effect.

The total plasma lipid rise in pregnancy is roughly one-third that found in jaundice and the phospholipids rise only a fraction as much in pregnancy as in jaundice. From these facts it may be concluded that while the rise in plasma lipids is common to jaundice and pregnancy, and while both improve rheumatoid arthritis, the magnitude of the plasma lipid level beyond a certain point is not contributory. Some observers feel that the improvement noted with pregnancy does not occur as regularly or as completely as with obstructive jaundice. In two such widely divergent states as jaundice and pregnancy with their many physiologic facets, the common lipemia may be the ameliorative factor in both conditions, in one, or in neither state. Further, an intimate disturbance in lipid metabolism may exist in these two conditions which is not mirrored by the relatively crude measurement of plasma lipids. We hope to investigate this latter potentiality.

Summary. In patients with active rheumatoid arthritis, the total lipid, the total cholesterol and phospholipid plasma content is normal; the calculated lipids and lipid ratios are normal.

The plasma lipid constituents and ratios of rheumatoid arthritics studied during gold salt therapy showed little change during the administration of this medicament.

The lipemia of pregnancy in patients with active rheumatoid arthritis is qualitatively and quantitatively similar to that of normal pregnant subjects. From the data in this paper it can be concluded that the ameliorative effect of pregnancy on rheumatoid arthritis is not dependent upon a correction of a lipid deficiency nor a shift in lipid ratios which is different in any way from that found in normal subjects during pregnancy.

The differences and the similarities of the lipemias of jaundice and of pregnancy have been delineated, from which it is concluded that the remission produced in rheumatoid arthritis by these two conditions is not brought about by the magnitude of the lipemia nor the inherent differences in cholesterol metabolism. The common ameliorative effect remains unexplained.

REFERENCES

1. Bayles, T. B.: Unpublished observations.
2. Bayles, T. B.: Unpublished observations.
3. Block, W. D., Buchanan, O. H., and Freyberg, R. H.: Arch. Int. Med., **63**, 18, 1941.
4. Bloor, W. R.: J. Biol. Chem., **77**, 55, 1928.
5. Boyd, E. M.: J. Clin. Invest., **13**, 347, 1934.
6. Boyd, E. M.: J. Biol. Chem., **101**, 323, 1933.
7. Entenman, C., Lorenz, F. W., and Chaikoff, I. L.: J. Biol. Chem., **134**, 495, 1940.
8. Epstein, E. Z.: Arch. Int. Med., **47**, 82, 1931.
9. Epstein, E. Z.: Arch. Int. Med., **50**, 203, 1932.
10. Epstein, E. Z., and Greenspan, E. B.: Arch. Int. Med., **58**, 860, 1936.
11. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem., **66**, 375, 1925.

12. Flock, E. V., Corwin, W. C., and Bollman, J. L.: Am. J. Physiol., **123**, 558, 1938.
13. Gorham, F. D., and Myers, V. C.: Arch. Int. Med., **20**, 599, 1917.
14. Hartung, E. F., Greene, C. H., and Bruger, M.: Proc. Am. Assn. for Study and Control of Rheum. Dis., p. 14, 1934.
15. Hartung, E. F., and Bruger, M.: J. Lab. and Clin. Med., **20**, 675, 1935.
16. Hench, P. S.: Med. Clin. North America, **24**, 1209, 1940.
17. Hench, P. S.: Proc. Staff Meet. Mayo Clin., **13**, 161, 1938.
18. Pemberton, R.: Arthritis and Rheumatoid Conditions, 2nd ed., Philadelphia, Lea & Febiger, 1935.
19. Pemberton, R., and Foster, G. L.: Arch. Int. Med., **25**, 243, 1920.
20. Schoenheimer, R., and Sperry, W. M.: J. Biol. Chem., **106**, 745, 1934.
21. Schwarz, O. H., Soule, H. D., and Dunie, B.: Am. J. Obst. and Gynec., **39**, 203, 1940.
22. Sperry, W. M.: J. Biol. Chem., **114**, 125, 1936.
23. Tyler, M., and Underhill, F. P.: J. Biol. Chem., **66**, 1, 1925.
24. White, F. W., Deutsch, E., and Maddock, S.: Am. J. Digest. Dis., **6**, 603, 1939.
25. White, F. W., Deutsch, E., and Maddock, S.: Am. J. Digest. Dis., **7**, 3, 1940.
26. Wilkinson, S. A.: Am. J. Digest. Dis., **3**, 618, 1936.

SICKLEMIA IN THE BLACK CARIB INDIAN*

By Thomas Hodge McGavack, M.D.
ASSOCIATE PROFESSOR OF MEDICINE
AND
William McKee German, M.D.
ASSOCIATE PROFESSOR OF PATHOLOGY
(From the Department of Medicine, New York Medical College, and the Department of Pathology, College of Medicine, Univ. of Cincinnati)

Sickle cell anemia is undoubtedly "the most common primary blood dyscrasia in negro hospital patients" of the southern United States.† Moreover, the sickle cell trait is seen in a high percentage of apparently normal negroes in this country, the actual figures varying with the individual investigator from 5.3%[16] to 14%[12] with an accepted average of about 7.5%. No studies of the sickling phenomenon appear to have been made on groups of negroes outside the United States.† The present report deals with a people who seem to have preserved wholly their integrity as a colored race, and among whom no cases of active sickle cell anemia have been identified in the hospital during the past 30-odd years.

Carib Indians at the San Juan village, 5 miles from the Tela Railroad Hospital at Tela, Honduras, were subjects of the present investigation. We were fortunate in receiving our introduction to them through one of their number who has attempted some detailed study of their

* These studies were carried out at Tela Hospital, Honduras, through the joint coöperation of the New York Medical College and the Univ. of Cincinnati, and under the auspices of the Association of American Medical Colleges and the John and Mary R. Markle Foundation. Appreciation for courtesy and help extended is also due Dr. Laurence A. Drennan, Chief of Staff, Tela Hospital, Honduras, and Mr. I. A. Dulsky, Director of Laboratories at the same institution.

† Since this manuscript was submitted for publication, an incidence of 15.5% sickling in physically fit, and 25% in sickly male West African soldiers has been observed by Evans (Evans, R. W.: The Sickling Phenomenon in the Blood of West African Natives, Trans. Roy. Trop. Med. and Hyg., **37**, 281, 1944). Abstr.—Biol. Abstr., **18**, 1171, 1944.

A second report (Mera, B.: Preliminares des estudio de la meniscocitemia en Colombia. Bol. of San Panamericana, **22**, 680, 1943; Abstr., Trop. Dis. Bull., **41**, 420, 1944) has just appeared stating that, of 489 negro school children examined in Puerto Tejada, Colombia, 46 (9.4%) proved positive for the presence of sickle cells. Of these, approximately 60% had sickle cell anemia, and the remaining 40%, the sickle cell trait.

origin. He recognizes 2 varieties of Caribs, the red and the black, and is sustained in this viewpoint by most authorities on the subject.[1,6,8,15,25]

Any exhaustive discussion of the origin of these 2 groups of Caribs is far outside the scope of this report. As a matter of fact, very little ethnologic consideration seems to have been accorded them. Kennedy,[15] Taylor,[25] Karsten,[14] and Currier[6] seem to be fairly well agreed, however, that the progenitors of these peoples came across the Atlantic from Africa, probably in sailboats of their own making, and apparently long before Columbus' epoch-making first voyage. They are still hardy sailors and are reputed to be the first peoples in the Western Hemisphere to use the sail as a means of power for propelling a boat. Taylor[25] describes the intermixture of the black Carib sailor and the Indian woman of the shores he invaded with the resultant development of the type to which the term red Carib has been given. Kennedy[15] emphasizes the purity of the black Carib who apparently continued to hold himself apart from any peoples with whom he came in contact. It is upon the blood of the black Carib that the present studies were made.

Some knowledge of his customs and moral standards only serves to emphasize the manner in which he has kept himself apart from all other people with whom he has come in contact.[14,15] The purity of his African ancestry is well demonstrated in the accompanying photograph which is an "at random" picture (Fig. 1). His features are characteristically negroid and without resemblance to other Indian tribes of North or South America. There is a heavy head of kinky, wooly, jet black hair. The skin varies in color from a chocolate brown to black, more commonly the latter. The forehead is wide; the eyes are keen with muddy yellowish (fatty) deposits in the scleræ; only occasionally are the cheek bones prominent; the nose is thick and flattened; the mouth is large, the lips thick, and the teeth well set and well preserved. Prognathism is not uncommon. Indeed, his resemblance to the African prototype is much more striking than that of his North American brother.

Material and Methods of Study. Of the 350 Carib Indians comprising the population of San Juan Village, Honduras, 300 were used as subjects. Of these, 133 were males, and 167 females. Their ages ranged from 4 months to 86 years, and are distributed numerically as follows:

TABLE 1.—AGE DISTRIBUTION OF SICKLING.

Years of age	No. of individuals	Individuals showing sickling	
		No.	%
0 to 4	42	5	11.9
5 to 10	42	7	16.7
10 to 19	76	4	5.2
20 to 29	47	5	10.6
30 to 39	46	2	4.4
40 to 49	20	0	
50 to 59	14	1	7.1
60 to 69	7	0	
70 to 79	2	0	
80 to 89	4	0	
Total	300	24	8.0

Blood smears were prepared on coverslips in the ordinary manner following puncture of the finger pad. They were then mounted on

microscopic slides and ringed with petrolatum to prevent drying. The slides were allowed to stand at room temperature (diurnal range from 72° to 87° F.) and were examined for sickling at approximately 2, 5, 18 and 24 hours after they were obtained. Resickling tests were carried out in a representative number, and in all instances in which there was doubt as to the change originally observed. Smears in which the cells failed to assume a characteristic form in this second trial were discarded as negative.

One hundred and thirty of the test subjects were questioned in regard to symptoms which might suggest that they had had acute episodes of sickle cell anemia. Specific questions were asked involving the recurrence, duration and severity of (*a*) joint and muscle pains, (*b*) "yellow eye-balls," (*c*) fever, and (*d*) abdominal pain. All persons with positive smears were interviewed at greater length.

Results. Twenty-four of the 300 individuals (8%), exhibited the sickling phenomenon in their red blood cells. The figures regarding age distribution are tabulated in Table 1, and those relating to sex and "sickling time," in Table 2.

TABLE 2.—TIME OF THE APPEARANCE OF SICKLING

	Positive smears				
	Male		Female		
Hours	No.	%	No.	%	Total
2	1	0 7	3	1 8	4
5	1	0 7	3	1 8	4
18	5	3 7	9	5 4	14
24	9	6 7	15	9 0	24

Sickling was observed in 9 of 133 males (6.7%), and in 15 of 167 females (9%). It was impossible to look for sickling immediately, but the low number of positives at the end of 2 hours and the statement of the director of the laboratories of the hospital that he had never seen sickling on ordinary blood smears would support the contention that the phenomenon is a rather latent trait among the group of peoples studied. The largest number (7) and the highest percentage (16.7) of positive smears occurred in the group between 5 and 10 years of age; in persons over 60 years old, the phenomenon was not observed; but neither of these variations is statistically significant.

Four of the 24 persons who shows sickled cells gave a history compatible with previous acute episodes of sickle cell anemia. However, in only 1 of these, a woman of 25 years, had icterus ever been noted. This had occurred but once at the age of 24, and was of such degree and character as to indicate definitely an attack of catarrhal jaundice rather than a crisis of the specific anemia. Histories were extremely difficult to evaluate in view of the prevalence of malaria and of intestinal parasites, either or both of which may produce disturbances symptomatically indistinguishable from the clinical syndrome found in sickle cell anemia.

Discussion. The present work was prompted by the following considerations: (1) The black Carib is a negro of relatively pure strain;

(2) sickling has not been studied in the tropics, nor indeed in negroes outside the United States; (3) the presence of sickle cell anemia in people not of the negro race has shown the necessity for careful evaluation of the statement that the disease arises from a hereditary racial trait; and (4) through 30-odd years, the records of one hospital in which Caribs are not infrequently patients fail to disclose a single case of identified sickle cell anemia.

1. The black Carib is a negro of relatively pure strain. We have adduced some evidence for this statement above; further pursuit of the subject can best be had by reference to Kennedy's article,[15] the conclusions in which are based upon both the author's personal observations and the writings of his contemporary and antecedent historians.

FIG. 1.—Group of Carib children, San Juan Village, Tela, Honduras.

2. Negroes outside the United States have not been previously studied for the sickling trait. It seemed important to do this, as the past emphasis upon the racial limitation of the disease has precluded any recognition of the possible influence of climate, habits of eating and living, the admixture of white or other blood, the presence or absence of intercurrent or concurrent disease, and so forth. The results obtained tend to support the race-linked character of the condition, for sickling was observed in 8% of the individuals tested, which is in close accord for such a small series with the average figure (7.5%) obtained on large numbers of persons studied in this country. Moreover, the sickling trait appears to be most prominent in the age groups at which the onset of sickle cell anemia has been observed in this country, between birth and 10 years, with an average of 6.3 years as determined by the review of 214 cases.[18]

3. Sicklemia and sickle cell anemia apparently occur in peoples not of the negro race, though, as has often been pointed out, it is practically impossible to exclude negro admixture absolutely, *i. e.*, to the extent required by the geneticist. Sickle cell anemia has been described in 26 Caucasians of birth or parentage as noted below. These include

14 persons of Sicilian or souther Italian origin;[2,3,9,10,11,19,20,21,22,29] an Arab boy;[1] 5 Greek children;[5,13,26,27] 1 Mexican Indian in whom negro blood seems to have been excluded;[28] 1 Cuban in whom negro blood may have existed;[24] and 4 persons whose families have been established in the United States for several generations.[4,17,23] When the cases are discarded in which there is doubt as to the diagnosis or the presence of negro blood in the immediate family, there remain 22 white patients with sickle cell anemia. Not only has active sickle cell anemia been noted in the white, but also the sickle cell trait has been observed among Indians who have had little opportunity for mixing with the negro. Killingsworth and Wallace[16] found sicklemia in 1.2% of female Mexican Indians but none among the men of the same tribe. These facts place the entire concept of race linkage in jeopardy.

On the other hand, the present study carried out in a tropical environment and on a hitherto unstudied tribe of African origin has yielded results so closely in accord with those obtained on North American negroes as to support strongly the hereditary racial character of the disease, despite its sporadic appearance in individuals who fail to show negroid characteristics or family histories.

4. No cases of sickle cell anemia have been recognized during the past 30-odd years among "not infrequent" admissions of Carib Indians to a competently staffed hospital. That cases were not overlooked seems to be supported by the fact that but 4 of 130 persons interviewed afforded any semblance of a history suggestive of acute attacks of the disease, whereas, 24 of these individuals exhibited the sickling phenomenon. However, it is extremely easy to overlook the disease. Of 214 reported cases, a mistaken diagnosis was made in 97, or 45.3%, and operations were performed on the basis of such diagnoses in 21 instances.[18] Further, the Carib is a very stoical individual, little giving to nursing his ills. It is well known that he almost never seeks outside medical care for malaria or intestinal disorders. It seems quite likely that by the same token he uses the tribal "doctor" or traditionally recommended herbs during his crises from sickle cell anemia.

On the other hand, do conditions in the tropics preclude the appearance of crises in people whose red blood cells carry the sickling trait? It seems unlikely that this question can be answered in the affirmative, as it has been shown by a number of investigators that the difference between sicklemia and sickle cell anemia is probably one of degree rather than one of kind. In both conditions the alterations occurring in the red cell are directly related to the oxygen tension and the hydrogen-ion concentration of the blood and tissues. There is little evidence to suggest that climatic conditions would seriously affect these factors.

Summary.—In wet, unstained preparations, the red blood cells of 24 of 300 Carib Indians of Honduras, Central America, showed the sickling phenomenon within a period of 24 hours. The sex and age incidence are noted. None of the individuals who showed sickling could be proved to have had active episodes of sickle cell anemia at any period of life. The significance of the findings is discussed, particularly in relation to the hereditary racial nature of the disease and

the sickling trait, and the environmental influences which may play a part in precipitating the crises.

REFERENCES

1. Archibald, R. C.: Trans. Roy. Soc. Trop. Med. and Hyg., **19**, 389, 1926.
2. Castana, V.: Pediatria, **33**, 431, 1925; Abstract, J. Am. Med. Assn., **84**, 1966, 1925.
3. Clarke, F.: Nebraska Med. J., **18**, 376, 1933.
4. Cooke, J. V., and Mack, J. K.: J. Pediat., **5**, 601, 1934.
5. Cooley, T. B., and Lee, P.: Am. J. Dis. Child., **38**, 103, 1929.
6. Currier, C. W.: Catholic World, p. 433, July, 1902.
7. Diggs, L. W.: South Med. J., **25**, 615, 1932.
8. Encyclopædia Britannica, 14th ed., **5**, 129; **19**, 862, 1937.
9. Greenwald, L., and Burrett, J. B.: Am. J. Med. Sci., **199**, 768, 1940.
10. Greenwald, L., Spielholz, J. B., and Litwins, J.: Am. J. Med. Sci., **206**, 158, 1943.
11. Haden, R. L., and Evans, F. D.: Arch. Int. Med., **60**, 133, 1937.
12. Hanson-Pruss, O. C.: J. Lab. and Clin. Med., **22**, 311, 1936.
13. Johnson, F. B., and Townsend, E. W.: South. Med. and Surg., **99**, 377, 1937.
14. Karsten, R.: The Civilization of the South American Indian With Special Reference to Magic and Religion, New York, Alfred A. Knopf, 1926.
15. Kennedy, J.: J. Ethnol. Soc. London, **4**, 226, 1856.
16. Killingsworth, W. P., and Wallace, S. A.: South. Med. J., **29**, 941, 1936.
17. Lawrence, J. S.: J. Clin. Invest., **5**, 31, 1927.
18. McGavack, T. H., and Nussbaum, C. C.: Urologic and Cutan. Rev., **46**, 194, 1942.
19. Mallory, T. B.: New England J. Med., **225**, 626, 1941.
20. Morrison, M., Samwick, A. A., and Landsberg, E.: Am. J. Dis. Child., **64**, 881, 1942.
21. Pontoni, L.: Hematologica, **20**, 657, 1939.
22. Rosenfeld, S., and Pincus, J. B.: Am. J. Med. Sci., **184**, 674, 1932.
23. Sights, W. P., and Simon, S. D.: J. Med., **12**, 177, 1931.
24. Stewart, W. B.: Am. J. Dis. Child., **34**, 72, 1927.
25. Taylor, D.: Natural Hist., **48**, 40, 1941.
26. Vance, B. M., and Fisher, R. C.: Arch. Path., **32**, 378, 1941.
27. Wade, L. J., and Stevenson, L. D.: Am. J. Path., **17**, 47, 1941.
28. Wallace, S. A., and Killingsworth, W. P.: Am. J. Dis. Child., **50**, 1208, 1935.

ARTERIOSCLEROTIC AND HYPERTENSIVE HEART DISEASE WITH RIGHT AXIS DEVIATION*

By A. H. Traum, M.D.

WASHINGTON, D. C.

(From the Cardiovascular Research Unit, Veterans Administration Facility)

The purpose of this study was to determine the prognostic significance of right axis deviation among patients with arteriosclerotic and hypertensive heart disease.

Material. Twenty-six patients with definite historical, clinical or necropsy evidence of either arteriosclerotic or hypertensive heart disease were used as the basis for this study. These cases were selected from 259 instances of right axis deviation found in the review of the electrocardiograms of 10,500 patients, taken between the years 1936 to 1944 at the Veterans Administration Facility, Washington, D. C. No patients were included in the analysis who revealed either clinical

* Published with the permission of the Medical Director of the Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

or autopsy evidence of rheumatic or congenital heart disease or cor pulmonale.

Approximately 70% of all the cases of organic heart disease treated at this hospital during the years covered by this study were due to arteriosclerotic or hypertensive heart disease.[1] The majority of the patients predominantly male, were veterans of World War I with an average age, at this time, of slightly over 50 years. There were 741 cases of hypertensive heart disease with 236 deaths, and 595 instances of arteriosclerotic heart disease with 119 deaths; of the total 1336 patients, 355 (26.5%) died in the hospital. Among the arteriosclerotic heart disease group, 241 patients were considered to have presented the clinical picture of a recent coronary thrombosis with myocardial infarction.

The average age of the group of 24 white males and 2 white females with right axis deviation included in this study was 51.73 years, with an age range from 32 to 65 years. These 26 patients comprised 1.9% of the total group of arteriosclerotic and hypertensive heart disease. Twenty-two of these cases comprised 3.7% of the arteriosclerotic group, and the remaining 4 patients comprised 0.5% of those with hypertensive heart disease. A record of any previous elevation of blood pressure or a persistent blood pressure reading above 140 mm. Hg systolic or 90 mm. Hg diastolic was considered sufficient to diagnose the existence of arterial hypertension. In the 4 cases of hypertensive heart disease encountered in this series the systolic and diastolic readings were well above these arbitrary limits.

Twenty-four patients presented typical historical and clinical evidence, including characteristic electrocardiographic findings, of coronary thrombosis with myocardial infarction. On 19 occasions the electrocardiograms were rather typical of anterior wall infarction, and in 5 instances the electrocardiographic changes were characteristic of posterior wall infarction. In 2 cases the probable location of the myocardial damage could not be satisfactorily determined (Table 1).

Cardiac enlargement was found by roentgenographic studies in only 5 cases. Four of these cases died during hospitalization and the clinical impression of cardiac enlargement, especially left ventricular hypertrophy, was verified in the 3 cases that came to autopsy. In 21 of the 26 patients studied, the heart was considered to be within normal limits as to size. In appraising this finding, the transverse diameter of the heart, the cardio-thoracic ratio, general contour of the cardiac silhouette and the phase of respiration as seen on the roentgenograms, and the results of physical examinations were taken into consideration.

Arbitrary criteria for the establishment of right axis deviation was adopted and closely followed. These criteria were: (*a*) S-1 must be larger than R-1 and R-3 larger than R-2; (*b*) the QRS conduction time must be within normal limits, namely, not greater than 0.1 second; and (*c*) the largest QRS complex should be greater than 0.5 millivolt in amplitude. No grossly out-of-phase records were included in this study. All of the tracings considered as revealing right axis deviation showed an angle above 96 degrees, and in all but 3 of the electro-

cardiograms the angle was above 110 degrees as determined by the method of Dieuaide.[4]

Each patient at some one time revealed a right axis deviation. Nine individuals did not show a right axis deviation on the first electrocardiogram taken; in 8 instances the electrical axis was normal and in 1 a left axis deviation was present. Seventeen patients revealed a right axis deviation on the first available electrocardiogram, this finding persisting throughout the period of hospitalization in 14 instances; in 8 of these 14 patients there was no change whatsoever in the configuration of the QRS complexes while there were changes in the ST segments and T waves. In the entire group a right axis deviation was noted on only 1 tracing in 8 patients during a series of electrocardiograms; on 4 occasions the right axis deviation noted was obtained on the last tracing of a series.

TABLE 1.—ANALYSIS OF CLINICAL FINDINGS IN HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE WITH RIGHT AXIS DEVIATION

			Clinical findings			Occlusion		Site of occlusion		Follow-up		
Case No	Age	Sex	Hypertension	Cardiac enlargement (Roentgen ray)	Myocardial infarction	Recent	Old	Anterior	Posterior	Alive	Dead	Duration
1	32	M	..	..	+	+	..	+	..	+	..	20 mos.
2	35	M	..	..	+	+	..	+	..	+	..	15 mos.
3*	38	M	+	+	+	..	+	+	..	+	..	1 mo.
4	42	M	..	..	+	+	..	..	+	+	..	26 mos.
5	44	M	..	..	+	+	..	+	..	+	..	41 mos.
6‡	46	M	+	+	+	+	..	+	..	..	+	51 mos.
7	46	M	..	..	+	..	+	+	..	+	..	64 mos.
8	46	M	..	..	+	+	..	+	..	+	..	22 mos.
9	48	M	..	..	+	..	+	..	+	+	..	31 mos.
10	48	M	..	..	+	+	..	..	+	+	..	51 mos.
11	50	M	..	..	+	..	+	+	..	+	..	58 mos.
12	51	M	..	..	+	+	..	+	..	+	..	35 mos.
13	52	M	..	..	+	+	..	+	..	+	..	54 mos.
14	53	M	..	..	+	+	..	+	..	+	..	56 mos.
15	54	M	..	..	+	+	..	+	..	+	..	44 mos.
16	54	M	..	..	+	+	..	..	+	+	..	22 mos.
17	56	M	..	..	?	..	..	?	..	+	..	7 mos.
18	57	M	..	..	+	+	..	+	..	+	..	28 mos.
19	58	M	..	..	+	+	..	+	..	+	..	23 mos.
20†	61	F	..	..	?	..	..	?	?	+	..	23 mos.
21	61	M	..	..	+	..	+	+	..	+	..	79 mos.
22‡	61	M	+	+	+	+	..	+	..	..	+	10 days
23	61	M	..	+	+	+	..	+	..	..	+	12 days
24‡	62	M	+	+	+	+	..	..	+	..	+	23 days
25	64	M	..	..	+	+	..	+	..	+	..	64 mos.
26	65	F	..	..	+	+	..	+	..	..	+	1 day
Totals	26	24 M 2 F	4	5	24	19	5	19	5	21	5	
Av. age	51.73											2.5 yrs.
Range	32 to 65 yrs.											1 day to 79 mos.

* Cardiac aneurysm.
† Hemiplegia.
‡ Autopsy.

All of the patients have been traced (Table 1). Five (19.2%) of the group died and autopsy examinations were performed in 3 instances; 21 patients are still alive. To date, the average duration of life among all of the patients is 2.5 years, with an age range from 1 day to 79 months.

The 3 cases which came to autopsy revealed cardiac enlargement with definite ventricular hypertrophy and coronary thrombosis and infarction in each instance. The heart weights were 435, 533 and 637 gm. An advanced degree of arteriosclerosis of the coronary arteries was found in all of the cases. Recent coronary thrombosis occurred once in the main right posterior coronary artery and twice in the left anterior descending artery.

Discussion. Klainer[7] was the first to attach any definite clinical prognostic significance to the findings of right axis deviation in hypertensive or arteriosclerotic heart disease. He concluded that the occurrence of right axis deviation with hypertensive or arteriosclerotic heart disease in the absence of rheumatic or congenital heart disease or cor pulmonale indicated a poor prognosis. Comeau and White[3] and Nathanson[9] have regarded right axis deviation in coronary heart disease as important in a negative sort of way. Comeau and White felt that the finding of right axis deviation is a strong though not conclusive evidence that the patient does not have coronary disease, and in such cases cor pulmonale particularly should be considered. Nathanson likewise concluded that the presence of coronary disease could be excluded on this feature alone, since most cases with primary right heart failure are associated with definite right ventricular preponderance. Nathanson reported that 2 out of 60 (3.3%) of the cases of coronary heart disease revealed right axis deviation. In a review of 200 cases showing right axis deviation, by Comeau and White,[3] it was found that 7 out of 125 (5.6%) of the cases with organic heart disease were due to coronary heart disease; these 7 cases constituted 10.9% of all organic heart disease over 30 years of age with right axis deviation. In the present study, electrocardiographic evidence of right axis deviation was revealed during the course of coronary heart disease without arterial hypertension, in 22 out of 595 (3.7%) of the cases. This percentage figure cannot be considered as insignificant when one of the most common cardiac diseases affecting adult man is under consideration.

The prognosis in those cases of arteriosclerotic heart disease with myocardial infarction was much more favorable than those with hypertensive heart disease (Table 1). Twenty of the 21 surviving patients had no evidence of cardiac enlargement or arterial hypertension. Four of the 5 that died revealed definite roentgenographic evidence of cardiac enlargement, and 3 of the 5 had hypertension. These findings were somewhat in agreement with those tabulated by Klainer.[7] In his series, 4 of the 5 known living patients revealed no evidence of hypertension or cardiac enlargement, and all 13 patients that were autopsied showed definite left ventricular preponderance. Among the 23 death cases reported by Klainer,[7] 15 had hypertension and 18 presented clinical evidence of cardiac enlargement.

XUM

Bohning and Katz[2] found that the few cases of right axis shift in patients with myocardial infarction were associated with anterior wall infarction. A definite trend in this direction was noted in the present series, in which 19 patients presented electrocardiographic findings compatible with anterior wall infarction and 5 cases showed evidence interpreted as indicating posterior wall infarction. Nineteen of the 26 cases presented evidence of a recent coronary occlusion; 3 of these 19 showed T wave negativity in all 3 standard leads of the electrocardiogram. Barnes and Burchell[1] have reported that the majority of cases of negative T waves in all 3 leads associated with right axis deviation occurred in cases in which there had been a recent coronary occlusion.

TABLE 2.—INCIDENCE OF RIGHT AXIS DEVIATION IN HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE

	No. of cases	% of total cases	Deaths	% of deaths
Hypertensive heart disease	737	99.5	233	31.6
Hypertensive heart disease with right axis deviation	4	0.5	3	75.0
Total hypertensive heart disease	741	100.0	236	31.8
Arteriosclerotic heart disease	573	96.3	117	20.4
Arteriosclerotic heart disease with right axis deviation	22	3.7	2	9.0
Total arteriosclerotic heart disease	595	100.0	119	20.0

One patient (Case 3) with an arterial hypertension and roentgenographic evidence of a left ventricular aneurysm revealed a right axis deviation that has persisted for 6 months. Eliaser and Konigsberg[5] found that right axis deviation occurred frequently in cases of ventricular aneurysms. These authors were unable to establish any correlation between the location of the aneurysm in the left ventricle and the electrical axis produced on the electrocardiogram.

The outcome, to date, of the patients with myocardial infarction without evidence of arterial hypertension and showing right axis deviation was much more favorable than that found in the entire arteriosclerotic heart disease group (Table 2). On the other hand, the small group of patients with hypertensive heart disease and right axis deviation revealed a more unfavorable prognosis than the entire group with hypertensive heart disease. There were 117 deaths (20.4%) among the 573 cases of arteriosclerotic heart disease, without evidence of either hypertension or right axis deviation; while only 2 (9%) of 22 similar patients with right axis deviation died. In the hypertensive heart disease group, 3 out of 4 patients with right axis deviation died; 233 (31.6%) of 737 cases without right axis deviation died during hospitalization.

The mechanisms involved in the cases with right axis deviation is not clear, and no adequate explanation could be made by an analysis of the 26 cases now being reported. Inasmuch as most of the patients revealed no evidence of cardiac enlargement or recognizable intraventricular conduction defects, other possible causes of the right axis

XUM

deviation must be offered. Pardee[10] and Hermann and Wilson[6] showed that the position of the heart in such instances may be an important factor resulting in a right axis deviation. Meek and Wilson[8] concluded that the rotation of the heart, while in its normal position, to the right on the anterior-posterior axis or to the left on the longitudinal axis of the heart will result in a right axis deviation in the electrocardiogram.

No close relationship should necessarily exist between the electrical R-axis and cardiac lesions known to exist beyond the main branches of the bundle of His.[12] This may be a factor in the finding of the right axis deviation in a large number of the cases reported in this series. Seventeen tracings showed a right axis deviation on the first tracing obtained and 14 of these showed a right axis deviation throughout the study. In these instances the right axis may have been present for sometime, and even before the existence of the cardiac condition. In a series of 200 unselected cases of right axis deviation,[3] 32.6% of all the cases above 30 years of age were thought to be in normal hearts. The right axis deviation present in a majority of the present series may have been coincidental findings in the clinical picture and actually indicated little if any involvement of the main branches of the bundle of His.

Conclusions. In the study of the data from a series of 26 cases of arteriosclerotic or hypertensive heart disease showing right axis deviation on the electrocardiogram, and without clinical evidence of valvular or congenital heart disease or cor pulmonale, the following conclusions were drawn:

1. Right axis deviation was not a common occurrence in the presence of arteriosclerotic heart disease, having been found in 22 (3.6%) of 595 arteriosclerotic heart disease cases.

2. Right axis deviation, when there is no cardiac enlargement, does not preclude a poor prognosis in arteriosclerotic heart disease. In this group of cases the prognosis was actually strikingly better than the entire group of arteriosclerotic patients encountered under similar hospital conditions.

3. In a small series of patients (only 4) with hypertensive heart disease the prognosis was unfavorable and definitely more serious than among the entire group of patients with hypertensive heart disease.

4. Right axis deviation, in patients with myocardial infarction, was more common in anterior than posterior wall infarctions.

REFERENCES

1. Barnes, A. R., and Burchell, H. B.: J. Mt. Sinai Hosp., **8**, 346, 1942.
2. Bohning, A., and Katz, L. N.: Arch. Int. Med., **61**, 241, 1938.
3. Comeau, W. J., and White, P. D.: Am. Heart J., **18**, 334, 1939.
4. Dieuaide, F. R.: Arch. Int. Med., **27**, 558, 1921.
5. Eliaser, M., and Konigsberg, J.: Arch. Int. Med., **64**, 493, 1939.
6. Hermann, G. R., and Wilson, F. N.: Heart, **9**, 91, 1922.
7. Klainer, M. J.: Am. J. Med. Sci., **199**, 795, 1940.
8. Meek, W. J., and Wilson, A.: Arch. Int. Med., **36**, 614, 1925.
9. Nathanson, M. H.: Am. Heart J., **5**, 257, 1930.
10. Pardee, H. E. B.: Arch. Int. Med., **25**, 638, 1920.
11. Reisigner, J. A., and Wilcox, B. B.: Med. Bull. Vet. Admin., **18**, 351, 1942.
12. Robb, R. C., and Robb, J. S.: Am. Heart J., **14**, 588, 1937.

THE INFLUENCE OF PITUITRIN AND EPINEPHRINE ON THE ACTION OF INSULIN ON BLOOD SUGAR

By Max Wishnofsky, M.D.
ADJUNCT IN METABOLISM, ASSISTANT PHYSICIAN

Arthur P. Kane, M.D.
ASSISTANT IN METABOLISM, CLINICAL ASSISTANT IN DIABETIC CLINIC

AND

Major Charles S. Byron, M.C., A.U.S.
ASSOCIATE IN METABOLISM, ASSOCIATE ENDOCRINE CLINIC
BROOKLYN, N. Y.

(From the Departments of Metabolism and Diabetes of the Jewish Hospital)

I. Pituitrin and Insulin. Textbooks on pharmacology, physiology and medicine accept the statement that pituitrin decidedly counteracts the action of insulin on blood sugar. Characteristic studies upholding this statement are exemplified by the following 2 articles. In 1923 Burn[3] observed that subcutaneous injections of extract of the posterior lobe of the pituitary gland, given simultaneously with subcutaneous injections of insulin, decreased or abolished the fall of blood sugar produced by the latter. He also found that pituitrin removed the symptoms of hypoglycemic convulsions, causing a rapid elevation of the blood sugar. He concluded from these studies that pituitrin is an antagonist of insulin. Davidoff and Cushing[4] confirmed the findings of Burn. In 3 patients suffering from acromegalic diabetes, who had been shown to respond normally to insulin, 20 units of insulin combined with 1 cc. of pituitrin were injected. The expected fall in blood sugar at the end of a 2-hour period did not occur. Geiling *et al.*[5] found the same to be true in dogs when insulin was given intravenously.

While the work reported here was in progress, an important contribution was made by Griffiths.[7] He showed that in rabbits posterior pituitary extracts invariably inhibited the hypoglycemia due to subcutaneous injections of insulin; but in many of the rabbits no antagonism to intravenously administered insulin was found. In other rabbits, however, the antagonism to intravenous insulin was well defined. He suggested that the antagonism between subcutaneously injected insulin and posterior lobe extracts is mainly due to a decreasing rate of absorption, probably as the result of the vasoconstrictor action of the pressor substance. Young[11] had previously made a similar postulation.

A review of the literature reveals that no work has been done on the influence of pituitrin on the blood sugar curve of diabetic patients receiving dextrose. We decided to do this work in the hope that our knowledge of the relationship between insulin and pituitrin would be clarified.

Before proceeding with the description of the experiments, it is important to note the following. It has been shown by us[10] that if equivalent amounts of dextrose and starch are given 2 days apart to a diabetic patient, the curves for the blood sugar contents of the blood

XUM

and urine will be identical. It is reasonable to assume that the same will hold true if equal quantities of dextrose are given 2 days apart. Consequently, if on one of the days of experimentation one new factor is introduced, such as the giving of pituitrin, any changes that may occur in the blood sugar curve must be considered significant.

EXPERIMENT 1. *Diabetic Patients Receiving Dextrose and Dextrose Plus Pituitrin.* Method of Procedure: Experiments were performed on 10 diabetic patients. To each of them, early in the morning after a fast of 14 hours, 70 gm. of dextrose were given orally in sufficient aqueous solution to constitute a total volume of 500 cc. Specimens of venous blood were taken at the fasting level immediately before ingestion, and 1 hour and 2 hours after the ingestion of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. Urine was collected 1 hour and 2 hours after ingestion of dextrose, and its sugar content determined by the Benedict method. Two days later an identical procedure was carried out with the following addition: Immediately before ingestion of the dextrose, also 1 hour later, 1 cc. of pituitrin* was injected subcutaneously.

Patients receiving protamine-zinc insulin abstained from it for 3 days immediately preceding the study, while those taking unmodified insulin abstained for 24 hours. No insulin was taken in the 2-day interval between tests. As will be seen subsequently in this experiment and in all the others that follow in which the same procedure was used, the fasting values on the 2 days of experimentation are identical. It may be assumed, therefore, that by this method the influence of exogenous insulin, previously administered, is completely eliminated.

TABLE 1.—BLOOD SUGAR IN DIABETIC PATIENTS (*a*) AFTER INGESTION OF DEXTROSE, AND (*b*) AFTER INGESTION OF DEXTROSE PLUS PITUITRIN

(1) 70 gm. of dextrose in 500 cc. aqueous solution.
(2) 1 cc. of pituitrin (10 International Units) subcutaneously, immediately before ingestion of dextrose and 1 cc. 1 hour later.

	Blood sugar (mg./100 cc.)						Urine (0 to 2 hours post cibum)					
	Fasting level		One hour post cibum		Two hours post cibum		Volume (cc.)		Sugar (%)		Sugar (gm.)	
Case No.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.	Dext.	Dext. + Pit.
1	331	322	605	555	588	540	430	285	3.8	4.6	16.3	13.1
2	317	328	488	476	548	506	225	250	5.0	3.7	11.3	9.3
3	247	250	526	520	526	500	423	310	4.2	4.1	17.8	12.7
4	292	282	414	413	414	476	322	310	4.0	4.8	12.9	14.9
5	140	118	256	330	178	392	210	140	1.3	4.2	2.7	5.9
6	171	178	314	258	374	..	164	108	5.0	3.0	8.2	3.2
7	294	260	440	413	408	513	350	285	5.0	4.7	17.5	13.4
8	219	204	404	435	388	409	332	275	4.6	4.6	15.3	12.7
9	181	172	298	272	317	334	242	142	4.5	4.1	10.9	5.8
10	163	170	308	312	308	388	615	298	1.5	2.5	9.2	7.5
Average	235	228	405	398	406	451	331	240	3.9	4.0	12.2	9.8

In Table 1 is shown the effect of pituitrin in diabetic patients on (1) the concentration of dextrose in the blood, (2) volume of urine, (3) concentration of dextrose in the urine, and (4) amount of dextrose in

* The pituitrin used was the Infundin of Burroughs, Wellcome & Co. Each cc. contains 10 International Units. The same preparation was used in all the other experiments which will be described below.

the urine after ingestion of 70 gm. of dextrose. It is evident that the blood sugar after ingestion of dextrose is not significantly greater when dextrose alone is given than when dextrose plus pituitrin are administered. The volume of urine when pituitrin and dextrose are given is significantly less than when dextrose alone is given, but not markedly so. The diuretic action of dextrose overcomes, to a great degree, the powerful antidiuretic action of pituitrin. The concentration of dextrose in the urine and the glycosuria are not significantly different. It is justifiable to conclude that pituitrin does not have any influence on the concentration of dextrose in the blood nor on the amount of dextrose in the urine in diabetic patients after the ingestion of dextrose. Apparently, pituitrin does not have any influence on the action of endogenous insulin.

EXPERIMENT 2. *Diabetic Patients Receiving Dextrose Plus Insulin (Subcutaneously) and Dextrose Plus Insulin (Subcutaneously) Plus Pituitrin.* In view of the findings made by Burn[3] and others, it was thought of interest to study the effect of pituitrin on the action of insulin given subcutaneously to diabetic patients receiving dextrose. Experiments were performed on 7 diabetic patients. The method of procedure was identical with that of Exp. 1, with the following modifications: Twenty units of unmodified U 40 insulin were given subcutaneously on the 1st day of experimentation ½ hour before the ingestion of dextrose. Two days later, insulin was again given in the same manner and, in addition, 1 cc. of pituitrin was injected subcutaneously immediately before the ingestion of dextrose and 1 hour later. The pituitrin and insulin were injected in different sites.

TABLE 2.—BLOOD SUGAR IN DIABETIC PATIENTS (*a*) AFTER INGESTION OF DEXTROSE PLUS INSULIN SUBCUTANEOUSLY, AND (*b*) AFTER INGESTION OF DEXTROSE PLUS INSULIN SUBCUTANEOUSLY PLUS PITUITRIN

(1) 70 gm. of dextrose in 500 cc. aqueous solution.
(2) 20 units of insulin subcutaneously ½ hour before ingestion of dextrose.
(3) 1 cc. of pituitrin (10 International Units) immediately before ingestion of dextrose, and 1 cc. 1 hour later.

	Blood sugar (mg./100 cc.)						Urine (0 to 2 hours post cibum)					
	Fasting level		One hour post cibum		Two hours post cibum		Volume (cc.)		Sugar (%)		Sugar (gm.)	
Case No.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.
1	294	280	358	400	342	460	160	284	5.0	6.0	8.0	17.0
2	288	308	151	370	65	364	42	170	1.0	3.8	0.4	6.5
3	252	284	308	440	377	470	109	248	4.2	4.6	4.6	11.4
4	200	181	189	204	131	210	340	126	0.0	1.0	0.0	1.3
5	131	118	106	113	70	86	60	62	0.0	0.0	0.0	0.0
6	163	167	205	286	118	340	368	187	0.0	0.8	0.0	1.5
7	220	236	367	318	262	421	270	350	3.3	2.9	8.9	10.2
Average	221	225	241	304	195	336	193	204	1.9	2.7	3.1	5.4

In Table 2 is shown the effect of pituitrin in diabetic patients receiving insulin subcutaneously on (1) concentration of dextrose in the blood, (2) volume of urine, (3) concentration of dextrose in the urine, and (4) amount of dextrose in the urine after the ingestion of dextrose. Allowing for the irregularities encountered, the blood sugar is greater

after the ingestion of dextrose plus subcutaneous insulin plus pituitrin, than when dextrose plus subcutaneous insulin alone are administered. This is especially evident 2 hours after ingestion of the dextrose. The same holds true for the amount of dextrose in the urine. These findings confirm the conclusions of Burn and others that pituitrin counteracts the action of insulin given subcutaneously.

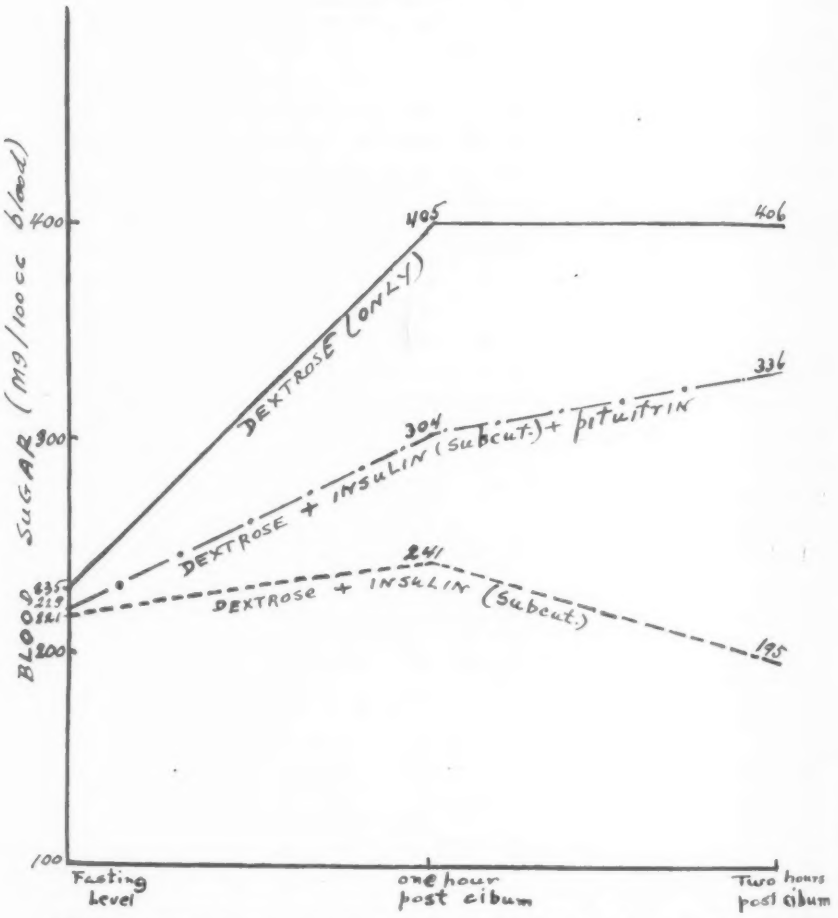


CHART 1.—Blood sugar curves in diabetic patients (1) after dextrose, (2) after dextrose plus insulin subcutaneously, and (3) after dextrose plus insulin subcutaneously plus pituitrin.

It is of interest to note to what degree pituitrin antagonizes the action of insulin given subcutaneously. The 10 diabetic patients of Exp. 1 (who received no insulin and no pituitrin on the 1st day of experimentation) have an average fasting blood sugar of 235 mg. per 100 cc. blood as compared to a fasting value of 221 in those of Exp. 2. These 2 groups may be considered identical as far as severity is concerned. Blood sugar curves, when the same amount of dextrose is

given to the 2 groups, would be practically identical. In Chart 1 are recorded the blood sugar curves where the following was given: Curve 1, 70 gm. of dextrose only; curve 2, 70 gm. dextrose plus subcutaneous insulin; curve 3, 70 gm. dextrose plus subcutaneous insulin plus pituitrin. It will be observed that whereas the blood sugar rises to 406 two hours post cibum when dextrose alone is given, it rises to only 336 when dextrose plus insulin plus pituitrin are administered. The conclusion is that, in the doses used, pituitrin only partially neutralizes the action of insulin on blood sugar.

Analysis of the results of Exp. 1 and 2 shows that pituitrin affects endogenous insulin and subcutaneously injected exogenous insulin differently. In Exp. 1, pituitrin apparently does not affect the action of endogenous insulin; in Exp. 2, however, the action of exogenous insulin is apparently counteracted. This led to the assumption that the mode of administration of insulin was significant. Accordingly, it was decided to study the action of pituitrin when insulin was given intravenously.

EXPERIMENT 3. *Diabetic Patients Receiving Dextrose Plus Insulin Intravenously and Dextrose Plus Insulin Intravenously Plus Pituitrin.* Method of Procedure: Experiments were performed on 8 diabetic patients. The method of procedure was identical with that of Exp. 1, with the following modifications. Fifteen units of unmodified insulin were given intravenously, immediately before ingestion of dextrose. Two days later, insulin was again given in the same manner and, in addition, 1 cc. pituitrin was given subcutaneously, immediately before the ingestion of the dextrose and 1 hour later.

TABLE 3.—BLOOD SUGAR IN DIABETIC PATIENTS (*a*) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY, AND (*b*) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY PLUS PITUITRIN

(1) 70 gm. of dextrose in 500 cc. aqueous solution.
(2) 15 units of insulin intravenously immediately before ingestion of dextrose.
(3) 1 cc. of pituitrin (10 International Units) immediately before ingestion of dextrose, and 1 cc. 1 hour later.

	Blood sugar (mg./100 cc.)						Urine (0 to 2 hours post cibum)					
	Fasting level		One hour post cibum		Two hours post cibum		Volume (cc.)		Sugar (%)		Sugar (gm.)	
Case No.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.	Dext. + Ins.	Dext. + Ins. + Pit.
1	165	184	98	87	128	111	165	80	0	0	0	0
2	240	226	180	144	109	116	128	95	0.8	0	1.0	0
3	388	345	320	206	328	180	95	90	2.5	2.0	2.4	1.8
4	336	318	156	265	280	342	25	45	0.5	1.4	0.1	0.6
5	248	256	197	195	100	166	60	55	0.5	1.7	0.3	0.9
6	234	256	97	129	152	171	58	52	0	0	0	0
7	270	267	140	125	129	188	44	57	0.8	1.3	0.4	0.7
8	276	261	111	212	252	276	61	0	2.0	0.0	1.2	0
Average	270	264	162	170	185	194	80	59	0.9	0.8	0.7	0.5

In Table 3 is shown the effect of pituitrin in diabetic patients receiving insulin intravenously on (1) concentration of dextrose in the blood, (2) volume of urine, (3) concentration of dextrose in the urine, and (4) amount of dextrose in the urine after the ingestion of dextrose. Analysis of the results reveals that pituitrin in no way affects the action of

insulin given intravenously on blood sugar and glycosuria in diabetic patients receiving dextrose. These findings are in striking contrast to those in Exp. 2, where insulin was given subcutaneously. They are in agreement with those made by Griffiths.

It has been shown by Goadby and Richardson that insulin, injected intravenously in rabbits, remains in the circulation in detectable amounts for about 90 minutes. In our patients, therefore, pituitrin was given the opportunity to counteract the action of insulin given intravenously. Such action, however, did not occur. We must conclude, therefore, that pituitrin does not antagonize the action of insulin.

By what means then does pituitrin counteract the action of insulin given subcutaneously? The first possibility that suggests itself is that pituitrin, by virtue of its vasoconstrictor action, retards the absorption of insulin from subcutaneous tissues. This is the theory entertained by Griffiths[7] and Young.[11] Indeed, this action of pituitrin has been utilized in "Deposulin," which is a mixture of insulin and pituitrin. It is claimed by Taeger and Danish,[9] Holland and Weger,[8] and Baudouin *et al.*[1] that the action of insulin is definitely prolonged as a result of this procedure. To avoid this local action of pituitrin, the insulin and pituitrin in our experiments were given subcutaneously in different sites.

Does pituitrin retard the absorption of insulin under these circumstances? This question can be answered in part by the following experiment. Phenolsulphonphthalein, injected subcutaneously, is absorbed into the circulation, excreted by the kidney, and its amount in the urine can be measured with exactness. Any retardation of absorption will manifest itself by a decrease in excretion by the kidneys. The following experiment was accordingly performed.

Method of Procedure: Experiments were performed on 6 normal adults. Each was injected subcutaneously with 1 cc. of solution containing 6 mg. of phenolsulphonphthalein. Each patient drank 500 cc. of water at the time of injection and 250 cc. 1 hour later. Urine was collected 1 hour and 2 hours after the injection of phenolsulphonphthalein. Two days later an identical procedure was carried out. In addition, 1 cc. of pituitrin was injected subcutaneously 5 minutes before phenolsulphonphthalein was injected, and 1 cc. 1 hour later. The pituitrin and phenolsulphonphthalein were injected in different sites. The phenolsulphonphthalein content of the urine was determined in the usual manner. The large quantity of water was given to insure an adequate excretion of urine, since pituitrin is a powerful antidiuretic.

In Table 4 are recorded the volumes of urine and amounts of phenolsulphonphthalein excreted during the 1st and 2nd hours after the injection of the phenolsulphonphthalein. The volume of urine is, of course, markedly less when pituitrin is injected. The amounts of phenolsulphonphthalein excreted, however, are not significantly greater when phenolsulphonphthalein alone is injected than when phenolsulphonphthalein and pituitrin are injected. The conclusion is clear that pituitrin does not retard the absorption of phenolsulphonphthalein from the subcutaneous tissues. An important consideration is the fact

that phenolsulphonphthalein has a very low molecular weight as compared with insulin, which is a protein. The absorption rate of the latter is much less than that of phenolsulphonphthalein. In view of the fact that pituitrin does not retard the absorption of phenolsulphonphthalein from the subcutaneous tissues, it is doubtful whether it appreciably retards the absorption of insulin; certainly not to a degree to account for the findings made in Exp. 2. It must be concluded, therefore, that the manner in which pituitrin counteracts the action of insulin given subcutaneously cannot, in the present state of our knowledge, be explained and awaits further research for its elucidation.

TABLE 4.—EXCRETION OF PHENOLSULFONPHTHALEIN, INJECTED SUBCUTANEOUSLY IN NORMAL INDIVIDUALS, IN URINE, WITH AND WITHOUT SIMULTANEOUS SUBCUTANEOUS INJECTION OF PITUITRIN

Pituitrin—1 cc. (10 International Units) injected 5 minutes before injection of phenolsulfonphthalein, and 1 cc. injected 1 hour later.
Water—500 cc. ingested immediately before injection of phenolsulfonphthalein, and 250 cc. 1 hour later.
Phenolsulfonphthalein—the amount injected was 1 cc. containing 6 mg. of the dye.

	Volume of urine (cc.)						P.S.P. excretion (%)					
	First hour		Second hour		Total 2 hours		First hour		Second hour		Total 2 hours	
Case No.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.	P.S.P.	P.S.P. + Pit.
1 . . .	135	60	385	62	520	122	38	26	23	21	61	47
2 . . .	133	80	610	60	743	140	17	27	32	14	49	41
3 . . .	340	55	376	45	716	100	14	43	18	22	32	65
4 . . .	237	57	550	30	787	87	32	31	23	17	55	48
5 . . .	185	60	703	50	888	110	22	25	26	16	48	41
6 . . .	190	28	380	30	570	58	49	43	16	2	65	45
Average . .	203	57	504	46	706	103	28.7	32.5	23	15.3	51.7	47.8

It is of interest to discuss the clinical value of these findings. The experiments reported here revealed an appreciable, but not striking, antagonism of pituitrin to the action of subcutaneous insulin on blood sugar. The dose of pituitrin used was 20 units during the 2-hour period of experimentation. The dose of insulin was comparatively small, only 15 units. The dose of pituitrin used here is far in excess of that employed clinically. This action of pituitrin is, therefore, chiefly of interest physiologically. It need not be taken into consideration in determining the dose of insulin in diabetic patients where pituitrin is being administered simultaneously.

II. Epinephrine and Insulin.—The literature on the action of epinephrine on blood sugar is enormous and need not be reviewed here. It is sufficient to state that it has been amply proved that epinephrine is an antagonist of insulin, as far as blood sugar is concerned. The remarkable difference in the action of pituitrin on insulin, given subcutaneously and intravenously, made us speculate as to whether such a difference in action also exists with epinephrine. The literature is replete with experiments on the action of epinephrine on insulin given subcutaneously. The only work on intravenously injected insulin is by Berg, Gross, McAfee, and Zucker[2] who found that epinephrine does not influence the blood sugar lowering effect of intravenously injected insulin in normal and depancreatized dogs. We decided to investigate this subject in human diabetics.

XUM

EXPERIMENT 5. *Diabetic Patients Receiving Dextrose Plus Subcutaneous Insulin and Dextrose Plus Subcutaneous Insulin Plus Epinephrine.* Method of Procedure: Experiments were performed on 6 diabetic patients. Each of them was injected subcutaneously with 20 units of unmodified insulin early in the morning after a fast of 14 hours. Each was given, orally, 70 gm. of dextrose ½ hour later in

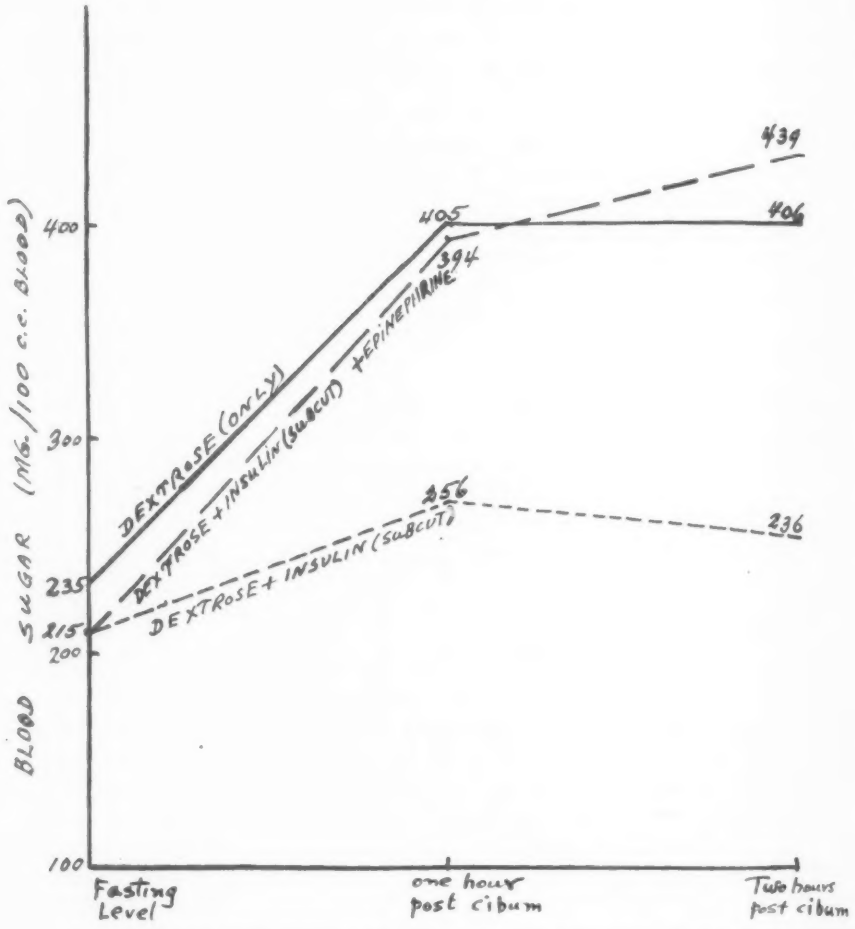


CHART 2.—Blood sugar curves in diabetic patients (1) after dextrose, (2) after dextrose plus insulin subcutaneously, and (3) after dextrose plus insulin subcutaneously plus epinephrine.

sufficient aqueous solution to constitute a total volume of 500 cc. Specimens of blood were taken at the fasting level, and 1 hour and 2 hours after ingestion of dextrose. The sugar content of the blood was determined by the Folin-Wu method. Two days later an identical procedure was carried out, with the following modifications. Ten minutes before the ingestion of the dextrose, also 75 minutes later, 10

minims of epinephrine hydrochloride (1 to 1000) were injected subcutaneously. Patients receiving protamine zinc insulin abstained from it for 3 days immediately preceding the study, while those taking unmodified insulin abstained 24 hours. No insulin was taken in the 2-day interval between tests.

In Chart 2 is shown the effect of epinephrine on blood sugar in diabetic patients receiving dextrose and subcutaneous insulin. The blood sugar values in Curve 2 are the averages (6 cases) when dextrose and subcutaneous insulin are given, while those in Curve 3 are the averages when dextrose plus subcutaneous insulin plus epinephrine are administered. It is evident that the blood sugar, after ingestion of dextrose plus subcutaneous insulin plus epinephrine, is markedly greater than when dextrose plus subcutaneous insulin alone are administered.

It was stated above that pituitrin in the doses used counteracted the action of insulin only partially. It is of interest to note to what degree epinephrine antagonizes the action of insulin. The 10 diabetic patients of Exp. 1 (who received no insulin and no pituitrin on the 1st day of experimentation) have an average fasting blood sugar of 235 mg. per 100 cc. blood, as compared to a fasting value of 215 in those of Exp. 5. These 2 groups can be considered almost identical as far as severity is concerned. Blood sugar curves, when the same amounts of dextrose are given, would be practically identical. In Chart 2 are recorded the blood sugar curves when the following are given: Curve 1, dextrose only; Curve 2, dextrose plus subcutaneous insulin; Curve 3, dextrose plus subcutaneous insulin plus epinephrine. It will be observed that Curves 1 and 3 are practically identical. The conclusion is that, in the doses given, epinephrine completely neutralizes the action of insulin on blood sugar.

EXPERIMENT 6. *Diabetic Patients Receiving Dextrose Plus Intravenous Insulin and Dextrose Plus Intravenous Insulin Plus Subcutaneous Epinephrine.* It was found above that pituitrin in no way influences the action of insulin, given intravenously, on blood sugar. It was considered of interest to make a similar study of the action of epinephrine on insulin given intravenously.

Method of Procedure: The method of procedure was identical with that of Exp. 5, with the following modifications: (1) Fifteen units of unmodified insulin were injected intravenously immediately before the ingestion of dextrose. (2) Ten minutes of epinephrine hydrochloride (1 to 1000) were injected subcutaneously immediately before the ingestion of dextrose and a similar dose 1 hour later.

In Table 5 is shown the effect of epinephrine on blood sugar in diabetic patients receiving dextrose and intravenous insulin. It is evident that the blood sugar, after injection of dextrose plus intravenous insulin plus subcutaneous epinephrine, is markedly greater than when dextrose and intravenous insulin alone are given. The conclusion is that epinephrine decidedly antagonizes the action of intravenous insulin on blood sugar; and to a degree almost equal to that of epinephrine on subcutaneously injected insulin.

TABLE 5.—BLOOD SUGAR IN DIABETIC PATIENTS (*a*) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY, AND (*b*) AFTER INGESTION OF DEXTROSE PLUS INSULIN INTRAVENOUSLY PLUS EPINEPHRINE

(1) 70 gm. of dextrose in 500 cc. aqueous solution.
(2) 15 units of insulin, intravenously, immediately before ingestion of dextrose.
(3) 10 minims of epinephrine hydrochloride (1 to 1000) 10 minutes before ingestion of dextrose, and 10 minims 1 hour later.

	Blood sugar					
	Fasting level		One hour post cibum		Two hours post cibum	
Case No.	Dext. + Ins.	Dext. + Ins. + Epineph.	Dext. + Ins.	Dext. + Ins. + Epineph.	Dext. + Ins.	Dext. + Ins. + Epineph.
1	272	320	288	514	308	482
2	320	374	149	380	127	460
3	203	154	213	300	226	395
4	353	280	218	385	154	423
5	337	326	500	469	500	517
Average	297	291	274	410	263	455

This action of epinephrine on intravenously injected insulin is in marked contrast to that of pituitrin which does not in the slightest, influence the action of intravenously injected insulin.

Summary and Conclusions.—1. Evidence is presented to negate the generally accepted opinion that pituitrin counteracts the action of insulin.

2. Experiments reported in this paper reveal the following: (*a*) Pituitrin does not influence the blood sugar curve of diabetic patients receiving dextrose. (*b*) Pituitrin definitely counteracts the action of insulin, given subcutaneously, on the blood sugar curve of diabetic patients receiving dextrose. In the doses used, the neutralization of the action of insulin on blood sugar was only partial. (*c*) Pituitrin does not, in the slightest, influence the action of insulin, given intravenously, on the blood sugar curve of diabetic patients receiving dextrose.

3. The fundamental conclusion to be drawn is that pituitrin is not an antagonist of insulin.

4. The theory has been advanced that pituitrin, by virtue of its vasoconstrictor action, retards the absorption of insulin given subcutaneously and, in this manner, prevents insulin from acting on the blood sugar. Experiments are reported which show that pituitrin does not influence the absorption of phenolsulphonphthalein injected subcutaneously. This theory is, therefore, untenable. The mechanism by which pituitrin counteracts the action of insulin, given subcutaneously, on blood sugar appears unexplained.

5. The action of pituitrin in partially neutralizing the action of insulin administered subcutaneously is of physiologic interest only. It need not be taken into consideration in determining insulin dosage in diabetic patients who are receiving pituitrin simultaneously.

6. Epinephrine markedly antagonizes the action of insulin, administered intravenously or subcutaneously, on the blood sugar of diabetic patients receiving dextrose. In the doses used, the neutralization of the action of insulin was complete.

REFERENCES

1. Baudouin, A., Lewin, J., and Azerad, E.: Compt. rend. Soc. de biol., **127**, 772, 1938.
2. Berg, B. N., Gross, J., McAfee, J., and Zucker, T. F.: Proc. Soc. Exp. Biol. and Med., **32**, 1358, 1935.
3. Burn, J. H.: J. Physiol., **57**, 318, 1923.
4. Davidoff, L., and Cushing, H.: Arch. Int. Med., **39**, 751, 1927.
5. Geiling, E. M. K., DeLawder, A., and Rosenfeld, M.: J. Pharm. and Exp. Ther., **42**, 263, 1931.
6. Goadby, H. K., and Richardson, J. S.: J. Physiol., **97**, 417, 1940.
7. Griffiths, M.: J. Physiol., **100**, 112, 1941.
8. Holland, G., and Weger, M.: München. med. Wchnschr., **85**, 215, 1938.
9. Taeger, H., and Danish, L.: Klin. Wchnschr., **16**, 1639, 1937.
10. Wishnofsky, M., and Kane, A. P.: Am. J. Med. Sci., **189**, 545, 1935.
11. Young, F. G.: Biochem. J., **32**, 1521, 1938.

THE EFFECTS OF ACETYL–BETA–METHYLCHOLINE IN HUMAN SUBJECTS WITH LOCALIZED LESIONS OF THE CENTRAL NERVOUS SYSTEM

By Stuart M. Fisher
CONSULTING PHYSICIAN, WESTMINSTER HOSPITAL
AND
George W. Stavraky
ASSOCIATE PROFESSOR OF PHYSIOLOGY
LONDON, CANADA

(From the Westminster Hospital and the Department of Physiology, Medical School, Univ. of Western Ontario)

In a recent paper by Stavraky[26] it was shown on experimental animals that aseptic removal of various portions of the cerebral hemispheres resulted in a prolonged sensitization of the remaining parts of the nervous system to intravenous injections of acetylcholine. This sensitization to chemical stimulating agents occurred in neurones which were directly connected with the removed portions of the brain and manifested itself in various specific patterns of response. Particularly striking results were obtained in cats in which the frontal lobes were removed (the motor cortex being included in the removal). Injections of acetylcholine in these animals resulted in characteristic motor manifestations and signs of excitation of the sympathetic nervous system, such as dilatation of the pupils, protrusion of the claws and erection of hair, all these phenomena occurring contralaterally to the removal.

In an extension of these experiments it was decided to study the effects of a suitable choline ester in human subjects with corresponding lesions of the central nervous system. Acetyl-beta-methylcholine was chosen in preference to acetylcholine because of its wide clinical use, extreme potency, and minimum nicotine-like action on the sympathetic ganglia. (Hunt and Taveau,[17] Hunt,[15] Villaret, Justin-Besançon, Cachera and Said,[27] Simonart,[23] Comroe and Starr,[6] Starr, Elsom and Reisinger,[24] Abbott,[1] Hunt and Renshaw,[16] Weiss and Ellis,[30] Myerson, Loman and Dameshek,[21] Dameshek, Loman and Myerson,[9] Altman, Pratt and Cotton[2] and others).

XUM

During the progress of the work it was found that best results were obtained with intramuscular injections of acetyl-beta-methylcholine instead of the subcutaneous ones employed in the majority of the previous investigations. The intramuscular injections gave quicker and sharper responses, the erythema and sweating often spreading down to the finger tips and toes of the tested subjects. As side effects of such injections, 3 of 19 persons became somewhat asthmatic, 1 complained of a feeling of tightness and pain in the chest, and 1 felt nauseated and experienced some pain in the epigastrium; all these symptoms were quickly relieved by a subcutaneous injection of 1/100 gr. of atropine sulphate.

The neurologic findings obtained with this method of study are in general agreement with the results reported in experimental animals and will be the subject of the present communication.

Methods. The effects of acetyl-beta-methylcholine chloride (Mecholyl Merck) were studied in 12 male patients with lesions of the rostral portions of the cerebral hemispheres or with signs of involvement of the upper motor neurones. The various lesions were: 2 brain tumors; 1 frontal lobectomy for a tumor; 7 head injuries in which damage was localized to the frontal lobe with or without extension of the injury to the motor cortex; 1 case of a lesion following an attack of cerebrospinal meningitis with residual signs of unilateral involvement of the pyramidal system; and 1 case of injury to the spinal cord. As controls, 6 normal persons and a patient with Raynaud's disease were studied in a similar manner.

Injections of 8 to 25 mg. of mecholyl dissolved in 0.3 to 1.0 cc. of distilled water were given into the deltoid muscle and were repeated in each patient at least on two or three occasions. The tested subjects were males of excellent physique, as they were associated with the armed forces of Canada. They were stripped and placed in a recumbent position on a table or a bed facing the window in order to obtain a dispersed and uniform lighting of the two pupils. The minimal amount of light in the ophthalmoscope necessary to produce a contraction of the pupils by flashing the light separately into each eye was then determined, and a complete neurologic examination was carried out before and during the action of mecholyl.

Results. *Effect of Mecholyl in Normal Males.* The sensitivity of different individuals varied considerably. As a rule, within 20 to 30 seconds after the injection of 8 to 10 mg. of mecholyl, the tested subject experienced a sensation of heat in the face. This was followed by a flushing of the face and neck, the erythema spreading rapidly to the chest and back and then to the extremities. It frequently extended to the fingers and toes but decreased in intensity towards the lower part of the body. An impression was gained that exposure to cold and possibly smoking or excitement had a tendency to cause an incomplete spreading of erythema over the apices of the extremities. The flushing reached its maximum about 2 minutes after the injection and was accompanied by widespread diaphoresis and often by rhinorrhea, salivation and lacrimation. Later in the response, shivering usually occurred and a slight increase of tendon jerks was occasionally noted. In 2 very sensitive individuals the first signs of flushing were accompanied by a slight transient dilatation of the pupils. Most of the features of the reaction described were terminated within 5 to 10

minutes after the injection, but larger quantities of mecholyl gave more pronounced reactions.

Effect of Mecholyl in Patients with Lesions of the Rostral Portions of the Cerebral Hemispheres. In 11 patients with lesions of the frontal lobe with or without involvement of the motor cortex, the injection of mecholyl produced an asymmetrical response. In 9 patients the erythema spread more rapidly on the side of the lesion and stopped in the upper extremity at the wrist or at the metacarpo-phalangeal joints, the hand or the fingers becoming very pale. In the lower extremity the flush extended to the ankle or to the dorsum of the foot. Contralaterally the spreading of the flush was delayed and the erythema stopped high on the limbs. Frequently the arm from the elbow down and the entire leg became pale, this pallor of the contralateral extremities developing more slowly than the ipsilateral flush. It became pronounced 2 minutes after the injection and reached its acme about 1½ minutes later, gradually replacing the initial erythema. In 3 patients the pallor spread almost over the whole side of the body opposite to the lesion, only the chest above the nipple line and the face remaining flushed on that side. About 3½ to 4 minutes after the injection, the contralateral blanching was often followed by a delayed flush, this occurring after the general erythema had largely subsided (see Fig. 1).

During the reaction the contralateral extremities were markedly colder than the ipsilateral ones. Also there was an asymmetrical distribution of sweating which was less pronounced on the side of the body opposite to the lesion. In the early stages of the response a delay in the sensation of heat on the opposite side of the face and a transient dilatation of the contralateral pupil were noted in 7 patients. In 4 of them both pupils dilated slightly but the contralateral effect was more marked. On 3 occasions the contralateral pupil became irregular in outline and did not constrict as readily to light as the ipsilateral one.

In cases in which the lesions extended to the motor or premotor cortex, muscular tremors, slight involuntary movements, an increase in spasticity, pronounced hyperreflexia, clonus of the wrist, ankle, and patella, and prominence of pathologic reflexes on the opposite side of the body characterized the later stages of the reaction.

The blanching of the extremities was most noticeable after the injection of 8 to 10 mg. of mecholyl, but the other features were more marked when larger quantities were administered. All the phenomena described were most pronounced in the case of lesions which involved the motor and premotor areas but a considerable asymmetry of the response was observed in frontally situated injuries in which no objective neurologic signs were present.

Three case reports of patients with different types of lesions will serve as an illustration. The first 2 cases demonstrate the reaction to mecholyl in a traumatic lesion of the motor cortex, and in a tumor involving the motor area of the brain. The 3rd case shows the effect of mecholyl after an injury to the premotor cortex.

XUM

CASE 1. Gnr. R.J., aged 21, on April 1, 1942 sustained a gunshot wound to the right side of the head. He was operated upon in England and on recovery was transferred to Westminster Hospital. When first seen on November 16, 1942, the patient had a typical hemiplegic gait and a scar which extended from a point anterior to the right ear to within 2 cm. of the midline. A depressed, pulsating bony defect 6 x 7½ cm. in area was noted under the scar.

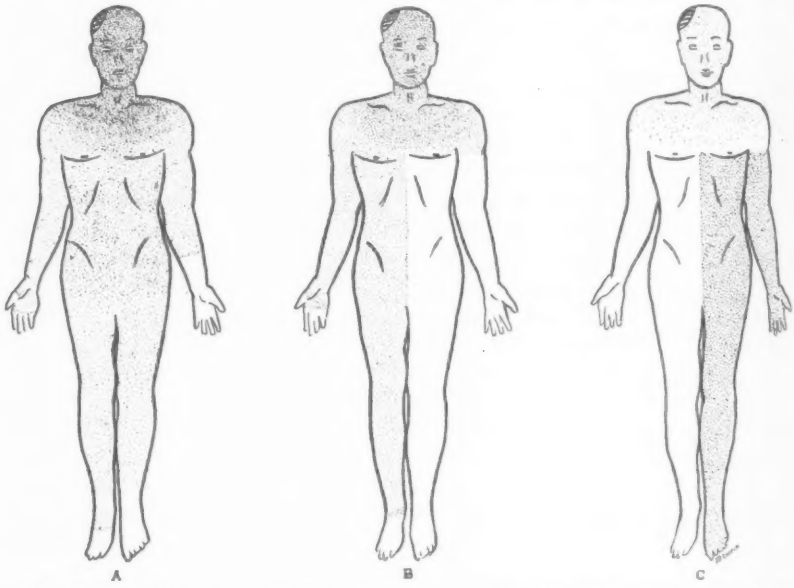


FIG. 1.—Distribution of erythema on intramuscular injection of 8 to 10 mg. of mecholyl in a patient with a left-sided hemiplegia resulting from a gunshot wound of the head. The bullet traveled from below up, destroying almost exclusively the motor area of the right cerebral hemisphere (Case 1). *A*, Distribution of erythema 1 to 2 minutes after the injection. *B*, Distribution of erythema 3½ minutes after the injection. *Note* the spreading pallor over the left side of the body. *C*, Initial erythema recedes 4 to 4½ minutes after the injection and a secondary flush appears over the previously pale regions on the left side.

On examination, a complete left hemiplegia was present involving the lower face, arm, and leg. Spasticity, increased tendon jerks, wrist and ankle clonus, plantar extension and a positive Hoffman sign, diminution of the corneal and abdominal reflexes, and a disturbance of cortical sensations were present at that time on the left side of the body. The paralyzed extremities felt clammy and cold and the left pupil was slightly larger than the right one, though both reacted to light. On November 5, 1943 when the patient was last examined, considerable recovery of sensation was noted in the paralyzed limbs, the corneal and abdominal reflexes were present and equal, the spasticity had decreased, the limbs being flaccid at the elbow and knee but a moderate spasticity of the hand and foot persisting. The pupils were of equal size, although the left one still had a tendency to dilate more briskly than the right one. In spite of the improvement the response to mecholyl was at this time even more asymmetrical than on the two previous occasions.

Effect of Mecholyl. (November 5, 1943). An intramuscular injection of 8 mg. of mecholyl was followed in 20 to 25 seconds by a sensation of heat in the right side of the face and by a slight but definite dilatation of the left pupil. Immediately following, the face, chest and extremities flushed rapidly and 2 minutes after the injection the erythema spread to the metacarpo-phalangeal

joints and to the dorsum of the foot on the right side. On the left side it extended to halfway between the wrist and the elbow, and to approximately 5 inches above the ankle, the left hand and foot becoming very pale and a sharp line of demarcation developing between the pallor and the flush. The pallor gradually ascended and 3½ minutes after the injection it had risen to 7 inches above the elbow on the left arm and involved the whole left leg and left lower portion of the body. The pale parts remained cold and dry, whereas the flushed regions were warm and covered with beads of perspiration. In half a minute the initial erythema largely subsided, whereas the pale hemiplegic parts of the body suddenly flushed. This delayed flush of the paralyzed side lasted less than 1 minute. At this time the spasticity of the paralyzed limbs was much greater than before the injection of mecholyl and there were tremors and some slight movements in the left arm. On another occasion an injection of 16 mg. of mecholyl resulted in much more pronounced tremors and athetoid-like movements in the paralyzed limbs and in an involuntary attempt to raise the stiffened semiflexed arm.

Case 2. L/Cpl. S.C., aged 49, on June 14, 1943 was admitted to the Westminster Hospital with a 2 weeks history of epileptiform attacks. The seizures were of a Jacksonian type, recurred at the rate of 2 or 3 a week and were largely localized to the left leg. The attacks were not accompanied by a loss of consciousness but they were associated with a "sickening feeling" in the epigastrium, and numbness and tingling in the left hand followed by weakness of the extremities on that side of the body. On examination a bronchogenic carcinoma was found in the left lung and the neurologic condition diagnosed as due to a metastatic tumor in the brain. The patient died on September 2, 1943 from pulmonary complications. The diagnosis was verified at autopsy, the primary carcinoma being situated in the upper lobe of the left lung and a metastasis of 4 x 6 cm. in cross-section was found in the precentral gyrus of the right cerebral hemisphere.

On July 2, 1943 preceding the injection of mecholyl, the patient was clear mentally, well oriented, and coöperative. Cranial nerves were negative except for a moderate sclerosis of the retinal blood-vessels Arcus senilis; tendon jerks were increased on the left side of the body with a suggestion of ankle clonus and positive Babinski and Oppenheim signs in the left foot; and the cremasteric and abdominal reflexes were diminished and easily fatigued on the left. All movements of the extremities were possible, but there was a definite weakness of the left hand and leg and the movements were awkward. There was also a slight wasting of the muscles of the left leg (right thigh 20¾″, left 20¼″; right calf 13½″, left 13¼″). The tone of the muscles of the left arm and leg was diminished and during walking the patient slightly dragged that leg while the arm hung limp, the associated movements being absent in it. There was no apparent sensory disturbance outside of some impairment of stereognosis and two point sensibility on the left.

Effect of Mecholyl (July 2, 1943). Twenty-five to 30 seconds after the injection of 10 mg. of mecholyl the patient experienced a sensation of heat in the face and neck which was followed by flushing of the face, the flush then spreading over the body. Three minutes after the injection the bright color extended symmetrically over both arms and the upper parts of the body, stopping on the hands at the metacarpo-phalangeal joints. On the right leg it descended to about 3 inches above the ankle, but stopped sharply at the left groin, the left leg remaining pale. Three and a half minutes after the injection, the lower left side of the body blanched rapidly and a sharp line of demarcation developed between the left and the right side of the chest and of the abdomen, the pallor stopping under the left nipple. The pale left side of the trunk and the left leg were cold and there was no sweating over these parts, whereas the flushed right half of the body was warm and densely covered with beads of perspiration. In half a minute the flush over the right side and over the upper left part of the body began to fade. The pallor over the lower part of the left side also wore off and was replaced by a delayed flush which lasted about a minute. A study of the reflexes at this time showed a greater asym-

metry of response on the two sides of the body than before the injection and a sustained ankle clonus on the left. The patient became asthmatic and 1/100 gr. of atropine sulphate was injected which quickly relieved the condition. After the administration of atropine the ankle clonus disappeared and could not be elicited on repeated examinations, but the plantar response remained extension on the left. No pupillary response of any kind was observed in this patient.

Case 3. LAC W.B., aged 20, on October 9, 1942 was hit on the head by an aeroplane propeller and was admitted to the Westminster Hospital on October 10, 1942 in an unconscious condition with a lacerated wound of the scalp 19 cm. long extending from 2 cm. posterior to the right orbit up to and over the midline of the vault of the head. The wound was explored, and loose fragments of bone, blood clots and oozing brain tissue removed, sulfanilamide powdered into the wound and the latter closed with interrupted sutures. The patient regained consciousness 48 hours after admission but had no control over the rectum and bladder for 22 days after the accident. For the next 2 months there was marked emotional instability and he exhibited a difference in the skin temperature on the two sides of the body, the left arm and leg feeling clammy and cold and the temperature in them being as much as 2° F. lower than in the extremities of the right side. For the same length of time the plantar response was extension on the left and flexion on the right side, this in the absence of any other abnormal neurologic findings except for a suggestion of a Horner's syndrome on the left.

Effect of Mecholyl (November 27, 1942). Twenty-five to 30 seconds after the injection of 8 mg. of mecholyl the patient experienced a sensation of heat on the right side of the face and there was a slight dilatation of the pupils, predominantly of the left one. This was followed by a flushing of the skin which in 2 minutes spread on the right side to the metacarpo-phalangeal joints and to approximately 5 inches above the ankle, whereas on the left side it extended to 3 inches proximal to the wrist and to the middle of the thigh, the lower parts of the extremities being very pale. About 3½ minutes after the injection the flush over the right side of the body receded while the lower left side of the body and left leg suddenly became pale and then flushed for a period of about half a minute. Simultaneously there was a slight change in the size of the pupils, the left one contracting and the right one seemingly increasing in size; then the right leg became flushed once more. Bilateral plantar extension, bilateral ankle clonus and patellar clonus on the right were elicited at this stage of the reaction (prior to the injection of mecholyl the Babinski sign was positive only on the left and no clonus was elicited at all). The injection was repeated on November 30, 1942 with similar results.

On December 18, 1942 preceding the patient's discharge from the hospital the temperature over the two halves of the body was practically equal and the neurologic examination negative, only a slight Horner's syndrome persisting on the left. On injection of 10 mg. of mecholyl the distribution of the erythema was almost symmetrical with some blanching of the hands and feet, but towards the end of the reaction there was an intermittent blanching and flushing of the two legs and a reappearance of bilateral ankle clonus, patellar clonus on the right and an indefinite plantar response on the left.

It is interesting to note that in the last case, upon the injection of mecholyl, the response was to a large extent bilateral. This bilateral distribution of various signs was even more striking in another case of extensive injury to both frontal lobes and must be regarded as an indication of a contre-coup damage of the opposite side of the brain. More difficult to understand was a case of an infiltrating brain tumor in which, as verified at autopsy, a medulloblastoma growing from the anterior part of the corpus callosum extended into the parietal and temporal regions of the right cerebral hemisphere and into the floor

of the left lateral ventricle. In this patient with a left sided hemiplegia, the injection of mecholyl caused a dilatation of the right pupil and a blanching predominantly of the right extremities.

Effect of Mecholyl in a Case of Spinal Injury. Mecholyl was injected into a patient recovering from a quadruplegia which followed a fracture dislocation of the cervical spine sustained in the collision of a staff car with a heavy gun during a blackout in England. The effect of mecholyl was so interesting that a brief case report and a description of the injection will be given.

CASE 4. Cpl. B.J., aged 42, on March 15, 1942, sustained an injury of the spinal cord at the level of the cervical 6 to thoracic 1 segments, resulting in an almost complete paralysis of a quadruplegic type. This was accompanied by a corresponding level of anesthesia and loss of bladder control. The diagnosis of a fracture dislocation of the 4th cervical vertebra was made. It was reduced surgically and the patient showed gradual improvement, regaining bladder control and partial function of his extremities. When seen on January 11, 1943 he could walk across the room without aid, but on examination showed considerable impairment of movements with bilateral spasticity, hyperreflexia, bilateral positive Hoffman and Babinski signs, and persistent sensory changes. All these findings were more pronounced in the upper extremities; in particular the recognition of passive movements in the fingers was grossly impaired but was good in the toes. The patient's chief complaint was that of a severe burning pain in the hands, which on examination looked very red, felt hot and perspired profusely.

Effect of Mecholyl. An injection of 16 mg. of mecholyl produced a symmetrical flushing which was more pronounced in the upper part of the body. However, in the upper extremities the erythema stopped 3 inches below the elbows, the color of the hands and lower forearms changing from bright red to pale purple. In addition, the hands became cool to the touch and dry, the perspiration on the palms and fingers stopping abruptly. The burning sensation of which the patient had complained so bitterly before the injection completely disappeared, all the signs returning 1½ hours later. Subsequently this patient was injected with various quantities of mecholyl (8 to 25 mg.) on numerous occasions, invariably obtaining some relief from the burning pain in his hands.

Effect of Mecholyl in an Angio-spastic Derangement. A somewhat similar response to mecholyl as the one noted in cerebral lesions was found to occur in a typical case of Raynaud's disease. In this patient mecholyl was injected during an angio-spastic attack which involved the index and middle fingers of the left hand. Preceding the injection the two fingers felt numb, were cold and had a wax-like appearance on the dorsal surfaces and blue-black patches on the palmar aspect. By the 2nd minute following the injection of 10 mg. of mecholyl the erythema spread over both hands, excluding the left index, middle and ring fingers and the right index finger, which all became very pale. On the right leg the flush descended to the ankle, but the left leg remained pale from the groin down. The erythema began to subside 3½ minutes after the injection, and when the right leg and the lower part of the body regained their normal color the left leg rapidly became flushed. Four to 5 minutes after the injection the pallor in the fingers gradually began to diminish and 2 or 3 minutes later the vascular spasm in the affected fingers of the left hand completely wore off and both hands acquired a normal appearance.

Discussion. The phenomenon of sensitization of denervated tissues to chemical stimulation is well known. In regard to the central nervous system Claude Bernard[3] drew attention to the fact that strychnine can cause movements in paraplegic limbs while Cannon,[4] Cannon and Haimovici,[5] and Stavraky[26] established experimentally that a selective sensitization to acetylcholine takes place in partially denervated neurones of the brain and spinal cord. The results obtained during the present investigation can be interpreted in the light of these findings.

In normal individuals mecholyl is predominantly parasympathicomimetic and probably its effects are largely of a peripheral nature. However, in cases of damage to the motor and premotor cortex as well as to the highest levels of the sympathetic nervous system (Fulton[11]), a sensitization to chemical agents takes place in the next links of the chains of descending neurones, and the sensitized neurones are stimulated by mecholyl to such an extent that their excitation overshadows the usual peripheral effects of this substance in certain parts of the body. If the sequence of vasomotor changes which occurs in patients with lesions of the frontal lobe following an injection of mecholyl is considered from this point of view, it may be suggested that first an erythema of a peripheral nature develops, then localized vasoconstriction sets in due to stimulation of sensitized sympathetic centers by mecholyl (the vasoconstriction occurring mostly contralateral to the lesion), and finally, when this latter subsides, a secondary flush appears in regions in which vasoconstriction interferes with the circulation, thus possibly leading to retention of mecholyl. The movements which occur in the paralyzed limbs, an increase of spasticity and an exaggeration of reflexes as well as other manifestations may be due to a sensitization of motor neurones.*

With the exeeption of the pupillary reaction, which varies, the effects of central stimulation develop slowly, and become prominent 2 to 4 minutes after an injection of mecholyl, the response in this way resembling that following intravenous injections of acetylcholine in the cat (Stavraky[26]). Protracted effects of injections of acetylcholine on the central nervous system have been noted also in intact animals. Keith and Stavraky[19] have shown in certain forms of experiments that acetylcholine prevents the onset of convulsions induced by thujone. Coombs and Cope[7] have confirmed this observation in regard to camphor and have emphasized the fact that the effect of acetylcholine on the central nervous system, after intravenous injections of the latter, persisted as long as 10 minutes, while Ellis and Weiss,[10] Lanari[20] and Harvey, Lilienthal and Talbot[14] observed that erythema and diaphoresis in an extremity lasted for 10 to 15 minutes after intra-

* Significantly, Cooper[8] in an attempt to treat upper motor neurone lesions with intraoral administrations of acetyl-beta-methylcholine, noted that an increase of spasticity took place in the paralyzed limbs. (A review of the literature on the question of treatment of neurologic conditions with choline derivatives can be found in a recent article by Ward, A. A., and Kennard, M. A., Yale J. Biol. and Med., **15**, 189, 1942.)

arterial injections of acetylcholine in human subjects. This slow type of response is particularly interesting in the case of the action of acetylcholine in view of its rapid rate of destruction in the body.

The blanching of the hands and discontinuance of sweating, as well as the relief from burning pain, which took place after the injection of mecholyl in the case of spinal injury (Case 4) were outstanding examples of the prolonged effect of mecholyl on sensitized nerve cells located in the isolated spinal sympathetic centers or peripheral sympathetic ganglia, the vasoconstriction caused by the stimulation of these structures probably accounting for the relief from pain and cessation of sweating, though as regards the latter, conditions may be more complex (Kahn and Rothman).[18]

The reaction in the case of Raynaud's disease had certain similarities with that observed in patients with lesions of the central nervous system. It is interesting that Starr[25] noted a different response to mecholyl given by injection or by the oral route in some peripheral vascular derangements, the former diminishing the circulation in the affected limbs while oral administration of mecholyl increased it. Page,[22] who suggested a central action of mecholyl, noted that upon subcutaneous injection it failed to cause vasodilatation in the hands and feet of hypertensive patients, whereas Goldsmith[12] observed a marked vasodilatation in the digits upon oral administration of mecholyl to a similar group of patients. Finally, Villaret and Even[28] and Villaret and Justin-Besançon[29] described a spectacular diminution of night sweats in tuberculous patients following injections of acetylcholine. This effect is most interesting inasmuch as in normal individuals acetylcholine causes an increased diaphoresis (Ellis and Weiss,[10] Harvey, Lilienthal and Talbot[14] and others). It appears possible that all these observations point to an increased irritability of certain groups of nerve cells to chemical agents in a variety of pathologic conditions as well as in the case of structural lesions of the central nervous system.

If this view is adopted, also the difference in the response to acetylcholine of epileptic patients and normal human subjects becomes readily understood. Williams[31] described a marked increase in the electro-encephalographic manifestations of epilepsy after injections of 0.25 mg. of carbaminoylcholine or 30 to 60 mg. of acetylcholine and presented a record of a clinical epileptic attack induced by means of an intravenous injection of 30 mg. of acetylcholine. No similar results could be obtained in normal controls, and in order to produce in non-epileptic human subjects (mental patients) tonic extensor spasm analogous to those described in intact cats (Stavraky[26]), Harris and Pacella[13] found it necessary to inject quantities of acetylcholine ranging from 220 to 500 mg.

Summary and Conclusions. In patients with lesions of the frontal lobe, intramuscular injections of acetyl-beta-methylcholine (Mecholyl) resulted in contralateral signs of excitation of the sympathetic nervous system, such as a slight dilatation of the pupil, and blanching, coldness

and diminution of sweating over the extremities and lower part of the trunk.

In cases in which the premotor and motor areas were involved, signs of excitation of the sympathetic nervous system were particularly prominent. In addition there were some motor manifestations, an increase of spasticity and the exaggeration of reflexes. All these occurred on the side of the body opposite to the lesion.

These effects of mecholyl are interpreted as resulting from a selective sensitization to chemical stimulating agents of partially isolated nerve cells situated in the chains of descending neurones of the brain and spinal cord.

The writers wish to express their thanks to Lt. Col. T. Morrison, Dr. A. Turnbull and the Staff of the Westminster Hospital for their helpful coöperation during the progress of this study.

REFERENCES

1. Abbott, W. O.: Am. J. Med. Sci., **186**, 323, 1933.
2. Altman, L. L., Pratt, D., and Cotton, J. M.: J. Nerv. and Ment. Dis., **97**, 298, 1943.
3. Bernard, C.: Leçon de Pathologie Expérimentale, 2nd ed., Paris, Baillière, p. 202, 1880.
4. Cannon, W. B.: Am. J. Med. Sci., **198**, 737, 1939.
5. Cannon, W. B., and Haimovici, H.: Am. J. Physiol., **126**, 731, 1939.
6. Comroe, J. H., Jr., and Starr, I., Jr.: J. Pharmacol. and Exper. Ther., **49**, 283, 1933.
7. Coombs, H. C., and Cope, O. M.: (*a*) Am. J. Physiol., **116**, 29, 1936; (*b*) Proc. Soc. Exp. Biol. and Med., **34**, 483, 1936.
8. Cooper, M. J.: Am. J. Med. Sci., **195**, 83, 1938.
9. Dameshek, W., Loman, J., and Myerson, A.: Am. J. Med. Sci., **195**, 88, 1938.
10. Ellis, S. B., and Weiss, S.: J. Pharmacol. and Exper. Ther., **44**, 235, 1932.
11. Fulton, J. F.: Physiology of the Nervous System, 2nd ed., New York, Oxford Univ. Press, p. 428, 1943.
12. Goldsmith, G. A.: Proc. Staff Meet. Mayo Clinic, **9**, 337, 1934.
13. Harris, M. M., and Pacella, B. L.: Arch. Neurol. and Psychiat., **50**, 304, 1943.
14. Harvey, A. M., Lilienthal, J. L., Jr., and Talbot, S. A.: Bull. Johns Hopkins Hosp., **69**, 529, 1941.
15. Hunt, R.: J. Pharmacol. and Exper. Ther., **6**, 477, 1914–15.
16. Hunt, R., and Renshaw, R. R.: J. Pharmacol. and Exper. Ther., **51**, 237, 1934.
17. Hunt, R., and Taveau, R. de M.: U. S. Hyg. Lab. Bull., **73**, 1, 1911.
18. Kahn, D., and Rothman, S.: J. Invest. Dermat., **5**, 431, 1942.
19. Keith, H. M., and Stavraky, G. W.: Arch. Neurol. and Psychiat., **34**, 1022, 1935.
20. Lanari, A.: Rev. Soc. argent. de biol., **12**, 207, 1936.
21. Myerson, A., Loman, J., and Dameshek, W.: Am. J. Med. Sci., **193**, 198, 1937.
22. Page, I. H.: Am. J. Med. Sci., **189**, 55, 1935.
23. Simonart, A.: (*a*) J. Pharmacol. and Exper. Ther., **46**, 157, 1932; (*b*) Ibid., **54**, 105, 1935.
24. Starr, I., Jr., Elsom, K. A., and Reisinger, J. A.: Am. J. Med. Sci., **186**, 313, 1933.
25. Starr, I., Jr.: Am. J. Med. Sci., **186**, 330, 1933.
26. Stavraky, G. W.: Trans. Roy. Soc. Canada, Sect. 5, **37**, 127, 1943.
27. Villaret, M., Justin-Besançon, L., Cachera, R., and Said: Ann. de méd., **32**, 385, 1932.
28. Villaret, M., and Even, R.: Presse méd., **36**, 1561, 1928.
29. Villaret, M., and Justin-Besançon, L.: (*a*) Lancet, **216**, 493, 1929; (*b*) Méd. J. and Rec., **132**, 35, 1930.
30. Weiss, S., and Ellis, L. B.: J. Pharmacol. and Exper. Ther., **52**, 113, 1934.
31. Williams, D.: J. Neurol. and Psychiat., **4**, 32, 1941.

SPONTANEOUS SPLENIC RUPTURE IN INFECTIOUS MONONUCLEOSIS

A Case and Pathologic Report

By Ward Darley, M.D., F.A.C.P.
ASSOCIATE PROFESSOR OF MEDICINE

William C. Black, M.D.
PROFESSOR OF PATHOLOGY

Charles Smith, M.D.
OUT-PATIENT PHYSICIAN, DEPARTMENT OF MEDICINE

AND

Frederick A. Good, M.D.
INSTRUCTOR IN SURGERY
DENVER, COLO.

(From the Departments of Medicine, Pathology and Surgery, Univ. of Colorado School of Medicine and Hospitals)

Infectious mononucleosis is usually a self-limited benign disease, but it may be complicated, as in the following case, by spontaneous rupture of the spleen.

Case Report. The patient, a 33 year old white male, American born, of English descent, occupation bank clerk, had been in good health and detailed questioning failed to reveal any history of splenic disorder. On May 19, 1943, he developed a mild sore throat and found that he was running a low grade fever. The sore throat subsided after 2 days but the fever persisted and gradually increased. He was first seen on May 30; chills, sweats and marked weakness constituting the chief complaints. The temperature was 100° F.; there was slight but definite tenderness in the upper right abdominal quadrant, otherwise the physical examination revealed nothing remarkable. By the next day, upper right abdominal pain was a conspicuous complaint, the liver edge was found to be 3 fingers' breadth below the right costal margin, and slight jaundice was noted. There was no lymphadenopathy.

The patient was hospitalized for observation. The admission blood count was as follows: hemoglobin 98% (Dare), red count 4,900,000, and the white count 7800 (75% neutrophils and 25% lymphocytes). The urine examination presented nothing abnormal except the presence of bile. The sedimentation rate was 19 mm. in the first hour. Agglutination tests for typhoid, paratyphoid, brucella and proteus OX–19 were negative.

On June 2 the white count was found to be 17,900 (40% each of neutrophils and lymphocytes and 20% large mononuclear cells). By this time jaundice was marked and the liver edge was 5 fingers' breadth below the costal margin. Exquisite tenderness was present in both upper abdominal quadrants. The inguinal and axillary lymph nodes had become enlarged and tender. The fever ranged from 100° to 101° F. Morphine was necessary for the control of abdominal pain. By June 3 the white count had risen to 34,300 (25% neutrophils, 58% lymphocytes—80% of which were large—and 17% large mononuclears). The heterophil antibody test (Paul and Bunnell) was positive at a dilution of 1:3584. Cervical lymphadenopathy was noted for the first time and the spleen was palpable 4 fingers' breadth below the left costal margin. Tenderness in the upper abdomen continued to be most marked.

Between the dates of June 3 and 5, the patient seemed to be improving as the jaundice, abdominal tenderness and fever were receding. At 6.30 A.M., however, on June 5, he was awakened from sleep by a stabbing, agonizing pain in the mid-epigastrium and back. He promptly went into shock. The

abdomen was rigid and tender. His condition steadily improved as 500 cc. of blood plasma and 1000 cc. of 5% glucose in normal saline were given intravenously. Because of the abdominal findings and symptoms, laparotomy was done 14 hours after the onset of the attack. The abdominal cavity was filled with blood which welled out of the incision, making inspection of the viscera impossible. By palpation a large tear near the hilus of the spleen was discovered, and the spleen was removed. Blood plasma was given throughout the operative period as fast as it could be made to flow (500 cc. in all). Surgery was followed immediately with another 250 cc. of plasma and then by 500 cc. of whole blood. Early the next morning another transfusion of 500 cc. of whole blood was given.* The condition of the patient throughout the operative and immediate postoperative period was surprisingly good. Twelve hours after the operation, the hemoglobin was 47%; red blood cell count 3,150,000, leukocyte count 30,800 (45% neutrophils, 54% lymphocytes, 1% eosinophils). Convalescence was satisfactory and the patient was discharged from the hospital on June 17. A blood count 1 month later was: hemoglobin 84%, red cell count 3,820,000 and white cell count 11,100 (45% neutrophils, 43% lymphocytes, 6% large mononuclear cells, 6% eosinophils). At this time the patient was up and about at will and he was discharged.

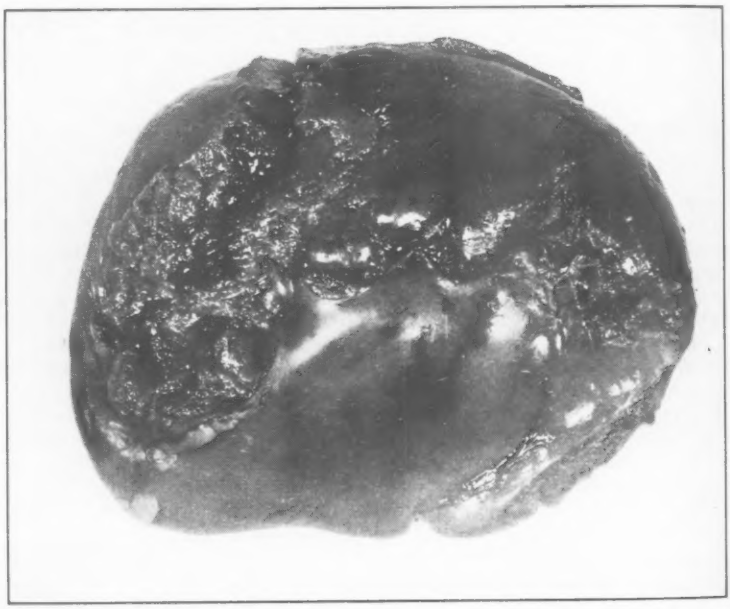


FIG. 1.—Convex surface of the spleen, showing torn capsule with protruding pulp.

Pathologic Report. The spleen weighed 460 gm., measuring 14.5 by 10 by 6 cm. The capsule was thin, smooth and tense. A ragged tear along the anterior margin, 4 cm. in length with protruding soft red pulp, was noted. This opening through the capsule extended obliquely across the convex surface for 2 cm. and measured 2.5 cm. in depth. Its margins were hemorrhagic in part, and surfaces made by cutting showed several solid masses of red blood clot embedded in the splenic substance of the region. These clots tended to be pyramidal in outline and measured from 0.5 to 2 cm. in their greatest dimension (Fig. 1).

* Blood plasma and whole blood were both obtained from the Belle Bonfils Memorial Blood Bank.

Surfaces exposed by cutting through the spleen at points removed from the rupture revealed a homogeneous dull red pulp, which tended to bulge and was soft and friable. Malpighian corpuscles were not grossly evident.

Microscopic Examination (Zenker's fluid and formalin fixation; stained with hematoxylin and eosin, phloxine-methylene blue, pyronin methyl green, and Giemsa; Bielschowsky, Foot's modification, for reticulum): Giemsa-stained impression smears from the unfixed spleen contained many small and large lymphocytes, and fewer neutrophilic and eosinophilic granulocytes.

The capsule and trabeculæ of the spleen appeared normal except where they had been distorted by hemorrhage into the adjoining substance. The reticulum appeared normal except where it was disrupted or hemorrhagic. The arterial branches and corpuscular arterioles appeared normal. The Malpighian corpuscles were small and lacked germinal centers.

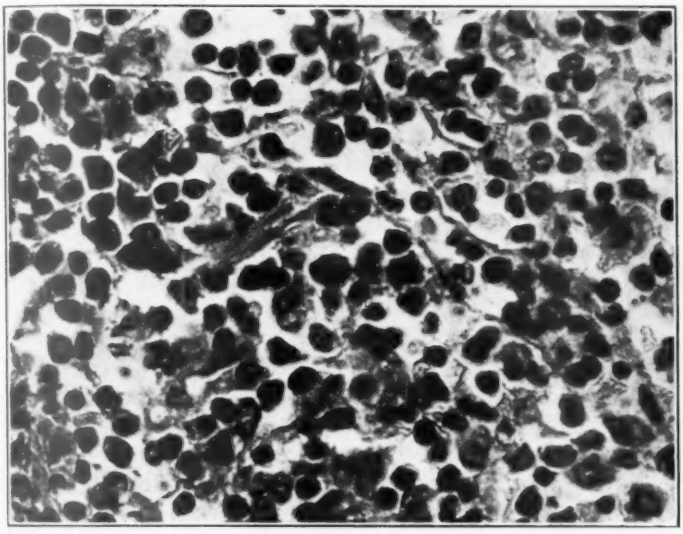


FIG. 2.—Section of red pulp showing large lymphoid cells with spheroidal nuclei, phloxine methylene blue stain (× 250).

The sinusoids were moderately full of blood containing many leukocytes, including neutrophils, occasional eosinophils and lymphoid cells. The distribution of cells between sinusoids and pulp spaces was nearly equal, and tended to obscure the sinusoidal boundaries. In general, the red pulp contained numerous small lymphocytes together with larger lymphoid cells having compact, spheroidal, deep staining nuclei and abundant non-granular cytoplasm (Fig. 2). Macrophages with indented, fusiform, or oval reticular nuclei and prominent nucleoli were also numerous. Phagocytosis of nuclear débris was evident in these cells. Plasma cells were present, and tended to occur in small clusters. A few large multinuclear cells resembling megakaryocytes were seen. Eosinophils were fairly numerous in the pulp spaces, while neutrophils were less common here than in the sinusoids. The endothelial cells lining the sinusoids were large, with faintly eosinophilic cytoplasm.

No definite evidence as to the direct cause of the fracture or hemorrhage in this spleen was obtained from the pathologic examination. It is possible that a local lesion previously existed at the site of the initial hemorrhage; but if so, it had been obliterated.

While the clinical course prior to the appearance of diagnostic signs and laboratory findings may have been obscure and unusually long,

the chief interest in this case centers around the spontaneous rupture of and the pathologic findings in the spleen of a patient with infectious mononucleosis. To our knowledge, the literature contains but 1 report of such a complication. In 1941, King[1] reported the case of a young man with infectious mononucleosis, who at the height of his disease suddenly developed the picture of an acute abdominal complication with shock. Splenectomy was performed and the patient recovered. The paper includes a pathologic study of the spleen by Dr. Shields Warren.

It seems probable that the spleen shares in the cellular change taking place in the lymphoid tissues during the course of infectious mononucleosis. These changes have been described by Gall and Stout[2] as consisting of 3 preëminent features: (1) marked proliferative activity in the pulp, which serves to obscure the margins of the follicles; (2) extensive but distinctly focal proliferative activity of clasmatocytes; (3) appearance throughout the pulp, on the edges of the germinal centers and in the sinuses, of large numbers of the specific "infectious mononucleosis cells." The use of Zenker-fixed nodes, stained with phloxine-methylene blue, aids in recognition of these cells, in the opinion of these authors.

Comparative studies of the spleen using a variety of stains, including phloxine-methylene blue, shows a general similarity to the changes described in lymph nodes. The follicular hyperplasia, which they describe as transient, was lacking in the spleen. The red pulp was crowded with lymphoid cells of all types, tending to obscure the sinusoidal structures, but evidence of proliferation of these cells *in situ* was not seen. Proliferative activity of clasmatocytes on a large scale was not demonstrable.

Large lymphoid cells corresponding to those described as "infectious mononucleosis cells" are fairly numerous in both the sinusoids and the pulp spaces, and are rather distinctively stained by phloxine-methylene blue.

A search for alterations in the stroma and vascular apparatus of this spleen revealed nothing of significance.

Conclusion. Spontaneous rupture of the spleen should be thought of when signs of a very acute intra-abdominal complication suddenly appear during the acute phase of infectious mononucleosis.

Pathologic examination of the spleen removed at operation disclosed rupture and hemorrhage with an increase in the lymphoid elements, and the presence of an atypical cell similar to that of infectious mononucleosis as found in the peripheral blood.

Since this report was submitted, another instance of spontaneous rupture of the spleen in infectious mononucleosis, with autopsy findings and histologic studies has been reported by E. E. Zeigler, Arch. Path., **37**, 196, 1944.

REFERENCES

1. King, R. B.: New England J. Med., **224**, 1058, 1941.
2. Gall, E. A., and Stout, H. A.: Am. J. Path., **16**, 433, 1940.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
G. LYMAN DUFF, M.A., M.D., PH.D.
STRATHCONA PROFESSOR OF PATHOLOGY, MC GILL UNIVERSITY
AND
E. G. D. MURRAY, O.B.E., M.A., L.M.S.S.A., F.R.S.C.
PROFESSOR OF BACTERIOLOGY AND IMMUNITY, MC GILL UNIVERSITY
MONTREAL, CANADA

THE RELATION OF STREPTOCOCCI TO HUMAN DISEASE: IMPORTANCE OF IDENTIFICATION AND NOMENCLATURE

I. THE BETA HEMOLYTIC STREPTOCOCCI OF GROUP A

BY J. HOWARD BROWN, PH.D.
AND
ISABELLE G. SCHAUB
BALTIMORE, MD.

(From the Johns Hopkins University School of Medicine, Department of Bacteriology)

THIS review is a plea for the recognition of bacterial species only in so far as the application of proper names yield clarity of thought and expression. No one knows what a bacterial species is. Among the higher plants and animals one has the aid of diverse morphology and the nonfertility of members of different species with each other. But among the bacteria the one is meagre and the other lacking. In his classical work on Immunity and Blood Relationship, Nuttall[18] (1904) showed that serologic results in large measure confirm zoölogic classification. Systematic bacteriologists find serology one of their most valuable tools. Nevertheless, they are still largely dependent upon physiologic activity, including pathogenicity, to differentiate one bacterium from another. If the minute structure of an enzyme or protein molecule could be seen, doubtless it would be found that diverse physiologic function is determined by morphologic difference. Biology is chemistry; chemistry is physics; and physics is the relation of objects in space, if there is any space. Every biologist assumes that species are relatively stable; they are the result of evolution which he has no reason to believe has been suspended, but which proceeds so slowly or so intermittently that it need not deter the giving of useful names to the species which he observes. Names are labels used for convenience in description and, if possible, to indicate genetic relationship.

Typhoid fever, diphtheria, tetanus, tuberculosis, plague, gonorrhea, anthrax, Asiatic cholera; these are specific diseases, each caused by a single species of bacteria. Because of this specificity, the identification of the microörganism with the disease and the ability to reproduce the disease experimentally serve to identify the bacterium although morphologic, cultural and serologic studies serve to make the description more

nearly complete and are valuable aids in bacteriologic diagnosis. Peritonitis, pneumonia, puerperal sepsis, sore throat, otitis media, arthritis, endocarditis, meningitis, osteomyelitis; these are not specific diseases and each may be caused by a number of different species of bacteria. The naming of a species of bacteria for a non-specific disease does not constitute an adequate description without morphologic, cultural and serologic studies.

Most of the streptococcal infections fall into the category of non-specific diseases. Furthermore, most of the pathogenic streptococci are "opportunist" pathogens, frequently harbored by normal individuals and producing disease only when opportunity is offered by accident, lowered resistance, or increased virulence of the microörganism brought about by passage through susceptible individuals. Of the human streptococcal diseases, the 2 which have the best claims for specificity are erysipelas and scarlet fever and yet, as will be seen, it appears that more than 1 species of streptococcus may cause each of these.

Streptococcus, as the name of a genus, was first used by Rosenbach[20] (1884) (Buchanan,[6] 1925) although previously many authors (Billroth, Cohn, Winge, Klebs, Rindfleisch, Von Recklinghausen, Crookshank, Orth, Pasteur, Koch, Ogston, Fehleisen) had observed cocci in chains and had used the name streptococcus or its equivalent as a morphologic term. In 1884 Rosenbach,[20] in a study of microörganisms from wound infections, employed the name *Streptococcus pyogenes*. Although Rosenbach's description was not adequate to distinguish this streptococcus from other species as we now know them, the source of his strains makes it highly probable that most of them were *Streptococcus pyogenes* as it is known today. Marmorek[17] (1902) noted that most of his strains of streptococci of human origin laked rabbit blood added to "peptone bouillon" and formed zones of hemolysis about colonies in blood agar. Andrewes and Horder[1] (1906) correlated the fermentation of sucrose, lactose and salicin, and failure to ferment mannitol with production of hemolysis. Lancefield[16] (1933) placed those of her strains of hemolytic streptococci which obviously were *Streptococcus pyogenes* in her serologic Group A. These may be regarded as the essential emendations to the description of *Streptococcus pyogenes* Rosenbach[20] 1884, *em.* Marmorek[17] 1902, Andrewes and Horder[1] 1906, Lancefield[16] 1933; a beta hemolytic streptococcus which ferments sucrose, lactose and salicin, does not ferment mannitol, and belongs to serologic Group A, although many other authors have added correlative and useful tests (Brown[4] 1919, Ayers and Rupp[2] 1922, Edwards[7] 1933, Tillett and Garner[23] 1933, Evans 1936[8]).

Streptococcus pyogenes, as defined above, is the species most frequently found in acute human streptococcal infections; including wounds, erysipelas, scarlet fever, septic sore throat, cellulitis, puerperal sepsis, septicemia, and sometimes in peritonitis, meningitis, endocarditis and many localized lesions. Less frequently one finds other beta hemolytic streptococci in many of these pathologic conditions.

It would be to the advantage of scientific medicine and bacteriology to have these differences recognized and reported rather than concealed under a single name. Too often simplification of nomenclature is attained by ignoring differences. Rolly[19] (1911–1912) introduced the name *Streptococcus hemolyticus* which has enjoyed considerable popularity. He did not state the sources of his strains nor did he report other characteristics than the appearances produced on blood agar plates. As a proper name *Streptococcus hemolyticus* has neither priority nor the historical definition of *Streptococcus pyogenes*. Some more recent authors have used *Strepto-*

coccus hemolyticus as synonymous with *Streptococcus pyogenes* while others apparently mean only a hemolytic streptococcus. The former should revert to the valid name; the latter should avoid the use of any proper name. Medical literature suffers much from such reports as Streptococcus hemolyticus Infection Successfully (or Unsuccessfully) Treated with Sulfonamides and advertisements of disinfectants which are claimed to kill *Streptococcus hemolyticus* within 1 minute. Which hemolytic streptococcus? Some are sensitive to sulfonamides and some are not. Some are more easily killed by disinfectants and heat than others.

Other hemolytic streptococci than *Streptococcus pyogenes*, some of them belonging to serologic Group A, are less frequently isolated from human infections. *Streptococcus infrequens*, as named by Holman[14] (1916), was a hemolytic streptococcus which fermented lactose, mannitol and salicin. Holman listed 29 strains from human sources. By the same definition, but adding positive fermentation of trehalose and sorbitol, Frost and Engelbrecht[12] (1940) reported 828 strains from milk and 76 strains from throats of dairy employees. The sources of Holman's strains make it possible that they might have belonged to either serologic Groups A or D. The strains of Frost and Engelbrecht might have belonged to Groups D or E, the fermentation of sorbitol, making probable the exclusion of those of Group A. From autopsies at the Johns Hopkins Hospital during six years (1932–1938) there were isolated 33 strains of beta hemolytic streptococci which fermented lactose, mannitol, salicin, trehalose and sorbitol; these probably belonging to Group D. Seven other strains differed in not fermenting sorbitol; these, in the light of later experience, probably belonging to Group A. During the next 5 years (1938–1943) serologic groupings of all beta hemolytic streptococci was carried out. In this period 40 strains, fermenting the 5 carbohydrates, were isolated; all belonging to Group D. Two other strains, differing in not fermenting sorbitol, were of Group A. This would indicate the probability that most of Holman's strains, also from human sources, were of Group D rather than Group A. The beta hemolytic streptococci of Group D have been adequately described by Sherman[21] (1937). Since Holman may have had one or more Group A strains among those which he described, *Streptococcus infrequens* Holman[14] 1916, *em.* Brown[5] 1939 may be emended to include only those beta hemolytic streptococci of Group A which ferment lactose, mannitol, salicin and trehalose but not sorbitol. Of the 9 strains mentioned above, isolated in this laboratory, 5 were from lungs, 2 from bronchi and 2 from heart blood.

Streptococcus erysipelatos was named by Rosenbach[20] (1884) although he gives credit for its discovery to Fehleisen[11] (1883). Rosenbach regarded *Streptococcus erysipelatos* as different from *Streptococcus pyogenes*, principally on the basis of minute colonial differences, but most authors have come to regard them as identical. Birkhaug[3] (1925) and Tunnicliff[24] (1926) consider *Streptococcus erysipelatis* a distinct species. Evans and Verder[10] (1938) found that some of Birkhaug's strains were of Group C, whereas erysipelas strains from other sources were of Group A. Since the strains of Fehleisen and Rosenbach cannot be identified, the name *Streptococcus erysipelatos* (or *erysipelatis*) should not be used without exact descriptive emendation.

Streptococcus scarlatinæ Klein[15] (1887) was applied to streptococci derived from cases of scarlet fever in England. Gordon[13] (1903–1907) and Andrewes and Horder[1] (1906) found that most of their scarlet fever strains fell into 2 fermentative groups, those which fermented salicin and

XUM

those which did not. Taking into consideration their hemolytic character, Andrewes and Horder regarded the former as *Streptococcus pyogenes* and named the latter *Streptococcus anginosus*, n. sp. Other differences (cultural, serologic and phageologic) also indicate that the salicin fermenting and non-fermenting streptococci from scarlet fever cases can hardly be regarded as of 1 species (Williams[25] 1932, Evans[9] 1937, Sherman[21] 1937). The question is further complicated by the existence of 2 serologic groups (A and G) among strains of *Streptococcus anginosus* Andrewes and Horder. The strains from scarlet fever apparently belong to Group A, while some from other sources belong to Group G. Obviously, the reasons which led Andrewes and Horder to reject the name *Streptococcus scarlatinæ* (*nomen ambiguum* or *nomen confusum*) would argue for the rejection of *Streptococcus anginosus*. The only way to conserve these names is to emend them in the light of recent discoveries. Evans[9] (1937) has proposed to do this for the salicin negative, scarlet fever strains of Group A and, if one follows her, the name should be *Streptococcus scarlatinæ* Klein[15] 1887, *em.* Evans[9] 1937. Since this would remove such strains from *Streptococcus anginosus* Andrewes and Horder[1] 1906, it would seem in order to confine the name *Streptococcus anginosus* to certain streptococci of Group G as suggested by Sherman[21] (1937). In any event, it must be borne in mind that *Streptococcus scarlatinæ* Klein[15] 1887, *em.* Evans[9] 1937 is not *the* streptococcus of scarlet fever but is *a* streptococcus of scarlet fever.

Streptococcus alactosus Brown[4] 1919, *em.* 1939 is a beta hemolytic streptococcus of Group A which ferments mannitol, salicin and trehalose but does not ferment lactose nor sorbitol. It liquefies human fibrin and does not hydrolyze sodium hippurate. The first strains, described by Smith and Brown[22] (1915), were from an institutional outbreak of sore throat in 1913; 2 of the strains from peritoneal pus and 2 from throats. Immune serum prepared against one of these strains agglutinated the others to high titer and did not agglutinate strains of *Streptococcus pyogenes* (*epidemicus*). Although this outbreak was described along with other "presumably milk-borne epidemics," there was no evidence that it was milk-borne. The streptococcus was not found in samples of milk from 25 cows supplying milk to the institution. So far as I know, this streptococcus has never been found in other than human pathologic material, and very rarely in that. During a period of 5 years it has been isolated twice from lungs at autopsy; both cases of lobular pneumonia following upper respiratory infections. One of the cases had been treated with sulfanilamide without satisfactory response. Under the name "Streptococcus hemolyticus II," Holman[14] (1916) reported 1 other strain of a hemolytic streptococcus which fermented mannitol and salicin but not lactose. It was from an abscess of the chest wall.

Conclusion. Named as emended above, 4 species of beta hemolytic streptococci of Lancefield's serologic Group A may be distinguished. They are as listed in Table 1.

It is realized that the relative prevalence might be quite different in material from other sources, *e. g.*, normal throats, intestines or the genito-urinary tract, or in material taken at different times or in other localities.

It might be convenient to regard species II, III and IV as "variants" of *Streptococcus pyogenes*, but is there any justification for it and would it be informative to have them so reported? If, as is commonly recognized by geneticists, variation in the direction of loss of characters is much more common than is the acquirement of characters, perhaps *Streptococcus infrequens* should be regarded as the parent species. Its infrequence is

no argument for or against its systematic significance; specimens of "missing links" may be rare. Although there may be experimental evidence that, after unusual treatment or prolonged selection, variation with respect to carbohydrate fermentation may occur, the fact remains that cultures of these species have been preserved for many years without evidence of variation. Furthermore, if variation occurs, it is important to recognize the variants; they may present differences in pathogenicity or in susceptibility to drug treatment. Only by the slow accumulation of exact records can these problems be solved. Our plea is less for correct nomenclature, desirable though it is, than for exact nomenclature. Opinions may differ regarding the former, but not the latter.

TABLE 1

	Dextrose (final pH)	Lact.	Mann.	Sal.	Treh.	Sorb.	Prevalence* at J. H. Hosp.
I. *S. pyogenes*	5.0±	+	−	+	+	−	83 strains
II. *S. infrequens*	5.0±	+	+	+	+	−	2 "
III. *S. scarlatinæ*	5.0±	+	−	−	+	−	3 "
IV. *S. alactosus*	5.0±	−	+	+	+	−	2 "

All 4 species are fibrinolytic for human fibrin and fail to hydrolyze sodium hippurate.
* Prevalence among 203 strains of beta-hemolytic streptococci isolated from autopsies at The Johns Hopkins Hospital during a 5 year period.

REFERENCES

(1.) **Andrewes, F. W.**, and **Horder, T. J.**: Lancet, **2**, 708, 775, 852, 1906. (2.) **Ayers, S. H.**, and **Rupp, P.**: J. Infect. Dis., **30**, 388, 1922. (3.) **Birkhaug, K. E.**: Bull. Johns Hopkins Hosp., **36**, 248, **37**, 85, 1925. (4.) **Brown, J. H.**: Monograph No. 9, Rockefeller Inst. for Med. Res., 1919. (5.) **Brown, J. H.**: Proc. of 3d Internat. Congress for Microbiol., p. 172, 1939. (6.) **Buchanan, R. E.**: General Systematic Bacteriology, Baltimore, 1925. (7.) **Edwards, P. R.**: J. Bact., **25**, 527, 1933. (8.) **Evans, A. C.**: J. Bact., **31**, 423, 1936. (9.) **Evans, A. C.**: J. Bact., **34**, 21, 1937. (10.) **Evans, A. C.**, and **Verder, E.**: J. Bact., **36**, 133, 1938. (11.) **Fehleisen, F.**: Die Aetiologie des Erysipels, Berlin, 1883. (12.) **Frost, W. D.**, and **Engelbrecht, M. A.**: The Streptococci, Madison, 1940. (13.) **Gordon, M. H.**: Lancet, **2**, 1400, 1905. (14.) **Holman, W. L.**: J. Med. Res., **34**, 377, 1916. (15.) **Klein, E.**: Report to Local Gov't. Board, **16**, 367, 1887; Proc. Roy. Soc., **42**, 158, 1887. (16.) **Lancefield, R. C.**: J. Exp. Med., **57**, 571, 1933. (17.) **Marmorek, A.**: Ann. Inst. Pasteur, **16**, 172, 1902. (18.) **Nuttall, G. H. F.**: Blood Immunity and Blood Relationship, Cambridge, 1904. (19.) **Rolly, F.**: Centralbl. f. Bakt., Abt. I, **61**, 86, 1912. (20.) **Rosenbach, F. J.**: Mikroörganismen bei den Wundinfektionskrankheiten des Menschen, Wiesbaden, 1884. (21.) **Sherman, J. M.**: Bact. Rev., **1**, 1, 1937. (22.) **Smith, T.**, and **Brown, J. H.**: J. Med. Res., **31**, 455, 1915. (23.) **Tillett, W. S.**, and **Garner, R. L.**: J. Exp. Med., **58**, 485, 1933. (24.) **Tunnicliff, R.**: J. Am. Med. Assn., **87**, 625, 1926. (25.) **Williams, A. W.**: Streptococci in Relation to Man in Health and Disease, Baltimore, 1932.

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF
JOHN E. GORDON, M.D.*
PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY, HARVARD MEDICAL SCHOOL
BOSTON, MASS.

VITAMIN DEFICIENCY AS AN EPIDEMIOLOGIC PRINCIPLE

BY W. LLOYD AYCOCK, M.D., AND GRACE E. LUTMAN, M.D.

IMMUNITY resulting from previous exposure to the infectious agent has long held first place in studies which seek an explanation for resistance

* On active service in the Armed Forces of the United States.

to infectious disease. It is clear that immunity from a previous infection, in measles, for example, affords resistance to subsequent infection. In other diseases, where some or even the majority of individuals, even though infected, never develop clinical disease, a favorite explanation has been subclinical immunity from "repeated bombardment with small subinfective doses." It has now become clear that in many diseases, other forms of resistance independent of antigen-antibody mechanisms play a major rôle.

Amongst the numerous hypotheses which have been considered to explain the inborn or acquired, constitutional or environmental, temporary or permanent, autarceologic resistance, faulty nutrition has become a generality.

"Clinicians generally agree that a deficiency in vitamins or other essential food elements usually results in a lowered natural resistance to bacterial infections," begins a recent editorial,[22] the occasion for which was the clear-cut experimental demonstration that a number of vitamin deficiencies as well as dietary depletion have the opposite effect—a marked increase in natural resistance to several virus infections.

The idea of dietary deficiency as a factor in resistance to infection seems to have for its foundation, first, the long association between famine and pestilence; and, second, the distinct association between vitamin A deficiency and xerophthalmia (not an infectious process itself, but frequently followed by secondary infection).

Famine and Disease. Countless references to famine are coupled with the phrase "followed by a plague or pestilence." One of the earliest notes occurred in 503 to 443 B.C. in India. "During the reign of the Emperor Tei-chund, extending over this period, there was a great pestilence and famine." Every century had at least one note of famine and plague, even through the 19th century. From 1193 to 1196 in England and France, famine was occasioned by incessant rains, and "the common people perished everywhere for lack of food, and in the footsteps of famine the fiercest pestilence followed, in the form of an acute fever." In 1600 in Russia—"famine and plague, of which 500,000 died," and so on.[115]

In many accounts of famines, the association between famine and fever, especially typhus, has been remarkable. Hirsch[45] observed "the coincidence in time between epidemics of typhus and the state of want brought about by failure of the crops, commercial crisis, war, and other far-reaching calamities." Chronicles of the pestilences of war and famine almost invariably included typhus fever as an immediate sequel to these disasters. Bateman[3] is credited with being the first to give definite expression to the opinion "that deficiency of nutriment is the principal cause of epidemic fever." "Famine and fever as cause and effect" was the title of an essay by Corrigan[16] following the Irish famine in 1846, and the idea of "hunger typhus" became more prevalent. It was a common observation that typhus appeared among the poor in proportion to the degree of want they had suffered. During the Irish potato famine those people who had had insufficient food were most frequently attacked, and this selection seemed to support the idea of infectious disease being directly dependent on lack of food.

These older concepts have survived to the present day; as, for example, in the observations of Zinsser, Castaneda and Seastone,[118] who found that guinea pigs and rats, subjected to vitamin-deficient diets to a point at which deficiency symptoms appeared and then inoculated with typhus virus, exhibited clinical pictures indicating a far more severe infection than that observed in normal animals after inoculation. There was also

a wider distribution of Rickettsiæ and a concentration of organisms that, in pleural and peritoneal exudates, amounted to almost cultural proportions. They remarked, "From the epidemiological point of view these experiments at least suggest an explanation of one of the important factors which enter into the historical association of high typhus mortality with war and famine."

Numerous other observers have attempted to place famine correctly as merely an indirect cause of epidemics of typhus, pointing out such other influences as overcrowding and lack of cleanliness. Several also have insisted that epidemics of typhus had frequently occurred in regions where there was no question of famine; and that at other times great famines were not followed by typhus. Ireland had suffered many famines, while typhus in epidemic proportions appeared in only a few of them.

This concept of the secondary rôle of famine in disease has been recently developed by Sigerist[86] who has supplied a logical sequence of events. During a time of famine, living conditions became poorer. Lice were more prevalent and once typhus started, it spread rapidly. Water supplies may have been neglected, what little food remained was not well controlled, and epidemics of cholera and dysenteric diseases resulted. Epidemics of plague often started following a drought that caused a crop failure. Rats moved closer to man to obtain food and, if plague was present, the disease was likely to be passed on to man. The same occurred following floods in which the crops, standing or harvested, were spoiled, and the rodents joined man to share in what food there was available.

Xerophthalmia. Severe deficiency of vitamin A with resultant xerophthalmia is almost unknown in the United States, and is common only in restricted areas in India and China. The loss of resistance to infections of various kinds in patients with xerophthalmia has been cited as a characteristic of this disease. Most reports show that a marked deficiency is associated with more numerous and severe infections. In 165 cases Blegvad[7] found 210 complications: pneumonia, bronchitis, otitis media, and so on. His cases undoubtedly suffered from a marked vitamin A deficiency, since they were clinical cases of xerophthalmia, but other deficiencies that very probably were present were not taken into consideration. Of Bloch's[10] group of 86 children with keratomalacia, 80% had infections of the respiratory tract, ear, urinary tract, or skin. He compared this group of patients with vitamin A deficiency with a group of 32 cases with scurvy. In the latter there were only 30% with infections. Only one case of pneumonia was present, in a patient with vitamin C deficiency who also had xerophthalmia. The other infections in the group of patients with scurvy, mainly mild catarrhal, cleared rapidly. Infections in the patients with vitamin A deficiency were not only more frequent but also more severe than those in the patients with vitamin C deficiency. Other[8,9] reports of small numbers of cases stressed the finding of the large percentage of infections seen in patients with vitamin A deficiency.

Spence,[89] on the other hand, found no increase in systemic infections in 17 cases of xerophthalmia studied over a period of 12 months. The 3 older patients had only the complaint of night-blindness, but the others had xerosis conjunctivæ, Bitot's spots, or commencing keratomalacia. The general health of the families of the 11 youngest patients had not apparently changed; the incidence of infection was not increased and lowered resistance was not indicated. A high incidence of skin sepsis, impetigo, and boils was present in 99 people examined in the families of these patients, but no increase in systemic infections.

XUM

In experimental studies of marked vitamin A deficiency and the resultant xerophthalmia without particular reference to concurrent infection, Emmett[26] found that, of 122 rats on low vitamin A diets, 98.2% developed xerophthalmia; and in Osborne and Mendel's[69] experiments using 136 animals on vitamin A free diets, only 69 (approximately 50%) developed the disease. This raised the question of possible variation in susceptibility in the several strains of animals. These experiments were performed primarily to show that xerophthalmia was not due to infection, but was a result of vitamin A deficiency.

Anti-infective Vitamin. The idea that vitamin A has properties that will increase resistance to infection has led to its being popularly called the "anti-infective" vitamin. It has been advocated especially by producers of vitamin products for the prevention of the common cold and similar infections. In 1935, the Council on Pharmacy and Chemistry of the American Medical Association defined its attitude toward the permissible claims which advertisers may make for vitamin A in cod-liver oil: "By virtue of its vitamin A content it promotes growth and, as indicated by experimental studies, may be an aid toward the establishment of resistance of the body to infection in general, though it has not been shown to be specific in the prevention of colds, influenza, and other such infections."[59]

Wolbach and Howe[113] in 1925 noted that the normal columnar epithelium of the nasal mucosa, trachea, etc., was replaced in vitamin A- and D-deficient animals by stratified keratinizing epithelium. Several factors were suggested as causes for increased susceptibility to infection. The reduction or absence of mucous membrane secretions that wash off bacteria and small epithelial particles would impair this mechanical action. Epithelial débris, especially in glands with blocked ducts, would provide a good medium for bacterial growth. The eye changes seen in acute vitamin A deficiency were considered due, at least in part, to infection on the grounds that resistance was impaired by vitamin A deficiency. However, from their work, Wolbach and Howe concluded that the substitution of keratinizing epithelium was not secondary to infection and that it probably was a primary effect due to withdrawal of factors necessary for the maintenance of differentiation of epithelium. The possibility that keratinization was secondary to the effects of vitamin deficiency on the metabolism of tissue was considered also. Mori[66] also had reported changes of the mucosa in rats deficient in fat-soluble vitamin A.

Cramer and Kingsbury[20] had concluded that a diet deficient in vitamin A impaired the efficiency of the local tissue defenses but did not apparently diminish the efficiency of the general defenses.

The loss of the protective powers of the epithelium due to diminished or absent mucus secretion and loss of ciliary motion was listed as one of the important predisposing factors to infection by Blackfan and Wolbach.[6]

Green and Mellanby[35] reported that young rats fed on diets rich in all known factors except vitamin A invariably died of some infective condition, especially local infections such as abscess at the base of the tongue, bronchopneumonia, infection of the genito-urinary tract, middle ear infection or similar lesions. The animals, unless too ill when treated, were cured by vitamin A. The results were so impressive and the specificity of the vitamin seemed so apparent that they called vitamin A the anti-infective vitamin. Mellanby[62] observed an epidemic of bronchopneumonia in his experimental puppies on a diet deficient in vitamin A, and found that the condition did not occur when cod-liver oil or butter was given to the animals. Vitamin A appeared to increase the resistance of the puppies

to bronchopneumonia. Two views of the mechanism of production of this increased resistance were taken: that the epithelial tissues were maintained in a normal condition by the fat-soluble vitamin and became hyperplastic and metaplastic and more susceptible to bacterial infection when they were absent; or that a local infection following vitamin deficiency caused hyperplasia of the epithelium. Mellanby and Green *et al.*[36,63] also studied the effect of vitamin A on puerperal septicemia with favorable results in the first cases. Later investigation did not show this benefit.

Rats were placed on diets low in fat-soluble vitamin A but adequate in other food elements in an experiment by Daniels, Armstrong, and Hutton[21] (16 test rats and 29 controls were used). The test rats were killed at varying intervals and the heads examined with special attention to the nasal mucosa. In all of the experimental rats, the nasal mucosa was covered with thick creamy exudate. The middle ears of 6 were examined, all of which were filled with pus; 3 had abscesses at the base of the tongue. Two rats after 9 and 11 weeks on the vitamin A-deficient diet were given cod-liver oil for 2 weeks, and then were killed and examined. Both of these had pus on the nasal mucosa and in the middle ears. One rat killed after 4 weeks on low vitamin A showed no inflammation of the nasal mucosa, while 2 others after 6 and 8 weeks on the deficient diet had marked nasal inflammation, and 1 also had pus in the middle ear and an abscess at the base of the tongue. Of the 29 controls, only 5 showed a little reddening of the nasal mucosa and no exudate, middle ear infection or abscesses at the base of the tongue. They concluded from their findings that fat-soluble vitamin A plays an important rôle in immunity to pyogenic infections, and that a general breakdown following diets low in the fat-soluble vitamin is secondary to this infection. Bacterial invasion of the mucous membranes of the nasal cavities and ear seemed to advance more easily when the diet was deficient. It has been assumed that some fats, especially cod-liver oil, have a beneficial effect in tuberculosis and some other infections, and the authors believed that the findings of this experiment seemed to provide evidence in support of these clinical observations.

McCollum[58] early described infection present in rats on a diet free from fat-soluble vitamin A.

Hess, McCann, and Pappenheimer,[44] Goldblatt and Benichek,[34] Turner,[100] Sherman and Burtis,[83] Macy and Outhouse,[56] Harris *et al.*[41] all found a high percentage of incidental infections in rats receiving a diet deficient in vitamin A.

Turner and associates[85,101] reported Gram-negative cocci present in the upper respiratory tracts and middle ears of rats suffering from lack of vitamin A. They were shown more frequently in the animals that showed the most severe symptoms of vitamin A deficiency. Tyson and Smith[102] noted infection always present even in the earliest stages of vitamin A deficiency and in late cases it was the predominant feature.

Torrance[97] found that feeding increased amounts of vitamin A to guinea pigs did not increase their survival time after injection of diphtheria toxin. Vitamin A assay of the livers brought out the fact that cod-liver oil had not increased the vitamin A storage. Later investigations,[98] using tetanus toxin, did not establish a correlation between the amount of vitamin A in the livers of guinea pigs injected with bacterial toxin and their length of survival time. The livers of animals from which bacteria were recovered at autopsy showed a lower level of vitamin A than in the livers of the guinea pigs that contained no organisms.

The amount of vitamin A in the human liver has been determined by

several workers (Laqueur, Wolff, and Dingemanse;[53] Wolff;[114] and Moore[65]). They found low values of vitamin A present generally in the livers of persons who have died from infections, but a rather wide range was seen in any infection or disease. The possibility that vitamin A stores are depleted from underfeeding or by infection should be considered. A decrease in blood carotene and vitamin A has been found by McCoord and Clausen.[60,104]

A great number of experiments with various organisms and using several techniques have been reported. McClung and Winters[57] found a marked increase in susceptibility to infection with *Salmonella enteritidis* injected intraperitoneally in a group of rats on a vitamin A-free diet for 7 weeks. Lassen[54] using vitamin A-deficient rats inoculated by mouth and subcutaneously with paratyphoid, reported a marked decrease in resistance of these animals as compared to rats on adequate diets. Vitamin A-deficient rats injected intraperitoneally with a bacillus of the mucosus capsulatus group in Boynton and Bradford's[12] study showed markedly decreased resistance to the infection but no increased susceptibility in rats on a vitamin D-deficient diet. Spindler,[90] infecting rats with *Nippostrongylus muris* and repeating the infection later, found that the animals deficient in vitamin A had had their resistance to superinfection markedly lowered. The effect of diet in epidemic infections in mice was studied by Topley, Greenwood, and Wilson.[96] They inoculated 25 mice with *B. ærtrycke*, put them into cages with 100 normal mice and observed them for 60 days. The addition of an excess of fat, butter or lard or a vitamin A concentrate seemed to produce an unfavorable reaction that was not shown when the mice were injected intraperitoneally. The addition of cabbage, carrots, or mangoes to an adequate diet did nothing to lessen the severity of the epidemic. They did not obtain any evidence that various additions to the diet increased resistance so as to produce a significant decrease in mortality under epidemic conditions.

Webster, in experiments the most striking result of which was success in the development of highly resistant or highly susceptible strains of mice to a given infection by selective inbreeding, tested the effect of nutrition on susceptibility. He found[109] that mice fed on a McCollum complete diet were more resistant to mouse typhoid, mercury bichloride intoxication and botulinus toxin than were similar mice fed on bread and pasteurized milk supplemented by an oatmeal and buckwheat mixture and dog biscuit. In Pritchett's experiments,[73] 5% butter fat or cod-liver oil added to a bread and milk diet appeared to increase the resistance of mice to *per os* infection with the paratyphoid mouse bacillus, but mice fed on a vitamin A-free fat diet showed no increased mortality as compared to those on a diet with cod-liver oil. In later experiments by Webster[108] with epidemics in mice he used variations from adequate to optimum constituents in the diet as one method of controlling the amount and severity of infection.

Greene[37] reported spontaneous infections with *B. pyocyaneus* in vitamin A-deficient rabbits and greater susceptibility to intravenous infection with Type 1 pneumococcus in these deficient animals than in normal controls. The vitamin A-deficient rabbits were more susceptible to intranasal infection with *B. lepisepticum* than control animals.

Microscopic lesions were reported in 100% of vitamin A-deficient rats by Gross,[38] although no clinical signs had been noted. Hou[48] also observed a high incidence of spontaneous infection in rats on vitamin A-deficient diets.

Rats and rabbits, suffering from lack of vitamin A, became less resistant to infection with the anthrax bacillus and the pneumococcus; but, as Werkman[110] pointed out, rats suffering from lack of vitamin B likewise were more susceptible to these infections, but since starvation also decreased their resistance, these results were not specifically due to vitamin A deficiency.

Evidence that there has been a visible decrease in morbidity statistics since the discovery and mass production and ingestion of vitamins is lacking. As Simmonds[87] has stated, "With the possible exception of pellagra, clear-cut clinically defined disease entities of dietary origin have not played a large part in mortality and morbidity statistics."

To summarize the results of investigations, indications are that vitamin A prevents a type of keratinization of tissues that is produced by deficiency of vitamin A, and reduces the possibility of secondary infection. In this way it might be termed "anti-infective" but there apparently is no effect on general immunity; and its therapeutic use in specific infections, *unless an actual deficiency is present*, has not been justified. The question of the influence of vitamin A on the epithelial tissues of the lung in pneumonia when there is a deficiency is controversial. Thus the evidence at present shows that vitamin A is not the only or most important factor in prevention of infection. "Anti-infective" vitamin with its present implications is a term which as yet does not appear to be justified.

One critic,[40] himself a nutritionist, sums up the situation in the following homely style, "Today vitamin A is often spoken of as the 'anti-infective vitamin,' and it is suggested that if you take enough of it it will prevent your catching coughs and colds, and the commoner infectious diseases, such as measles, chickenpox, or scarlet fever, etc. It is even claimed (as you will have noticed if you read the advertisements) that should you have already caught one of these infectious diseases a dose of vitamin A will help you to recover quickly."

"How did this theory start? Well, it was known that animals dying from vitamin-A deficiency became infected, and it was assumed rather too easily that a kind of generalized converse was true also, that is, that 'infections are due to vitamin-A deficiency.' The logic of course is at fault, and the theory also in my opinion is at variance with the known facts. . . . The position therefore in a nutshell is this. If you take insufficient vitamin A, you are certainly liable to develop special kinds of localized infections. It is wise, therefore, to take care that your diet is adequate and well-balanced. But this has nothing to do with ordinary infectious diseases as commonly met with; and in any case most people in this country do appear to get ample vitamin A, so that in such circumstances it seems futile to try and treat ordinary infectious diseases and septicæmias with vitamin-A medication."

Vitamin B deficiency and susceptibility to several infections have been studied by many workers. Badger, Masunaga, and Wolf[1] obtained evidence that rats on a thiamin-deficient diet were more susceptible to rat leprosy than were normal rats. Rose and Rose[78] injected dogs partially deficient in vitamin B with *Staph. aureus*. They found that they appeared more susceptible to deleterious effects of artificial infections with *Staph. aureus* and the survivors had positive blood cultures longer than the controls. Pemberton and Bessey[70] reported that riboflavin-deficient rats showed loss of resistance to murine typhus. Rats on a vitamin B complex-free diet and infected with an enteritidis organism had 19% survivors as compared to 75% survivors with brewers yeast added to their diet in an

experiment by Ross and Robertson.[79] Rats on a diet deficient in either riboflavin or thiamin and infected with *Nippostrongylus muris* showed a marked reduction in resistance in Watt's work.[106]

Wooley and Sebrell[116] reported that mice deficient in riboflavin or thiamin were more susceptible to a fatal infection with pneumococcus Type 1 inoculated intranasally than mice on an adequate diet. They carried out paired feeding experiments to show that this increased susceptibility was not due to a restricted food intake. Large amounts of riboflavin or thiamin given at the time of inoculation did not reduce mortality in the deficient group.

A life-long deficiency of vitamin B_1, in rats resulted in a shortened duration of life and decreased reproduction in a study by Drummond and associates.[24] The incidence and severity of chronic lung infections, as well as other disorders and tumors was not influenced by the vitamin deficiency.

Increased resistance to ulcerative cecitis of rats on a diet deficient in the vitamin B complex was observed by Bloomfield and Lew.[11] The controls on a normal diet had an incidence of 50% of cecitis and the animals deficient in the B complex showed insignificant lesions in 19%. The cause of cecitis is questionable, many of its features suggesting a virus disease.

Vitamin C-deficient diets have been shown to increase the susceptibility of guinea pigs to various infections. Theobald Smith[88] noted pneumococcus pneumonia in his guinea pigs, which was controlled by adding green fodder to the diet. Findlay[27] reported that guinea pigs fed on a diet deficient in vitamin C succumbed to a smaller infecting dose of the pneumoccocus, *Staph. aureus*, *Strep. hemolyticus*, and *B. coli*, and Werkman, Nelson, and Fulmer[111] found that vitamin C-deficient guinea pigs revealed a definite though not marked break in resistance to infection by the pneumococcus and *B. anthracis*, but no difference in their ability to produce specific agglutinins for the typhoid bacillus as compared with healthy animals. Markedly scorbutic guinea pigs showed a drop in resistance to *B. necrophorum* in McCullough's[61] experiment. Avirulent human strains produced minor abscesses in these deficient guinea pigs although no reaction was evident in animals on adequate vitamin C diets. McCullough noted that a severe scorbutus was necessary before a drop in resistance became evident. Chronic subscurvy with a superimposed Beta hemolytic streptococcus infection that produced an arthopathy similar to that of rheumatic fever and rheumatoid arthritis was reported by Rinehart, Connor and Mettier.[75,76] They suggested that a subclinical degree of scurvy may make up the rheumatic tendency which, with an added factor of infection, causes the development of rheumatic fever or rheumatoid arthritis.

The addition of vitamin C and other vitamins to the diets of children with rheumatic fever did not reduce the incidence of upper respiratory infections, and there has been no correlation between rheumatic fever and scurvy.[51] In tuberculosis[72] and some other infections, more ascorbic acid than average apparently is needed to maintain a high plasma level; however, there is no evidence that a deficiency of vitamin C causes susceptibility to infection. Pijoan and Lozner[71] recently have concluded that ascorbic acid has but two known uses: the prevention and the treatment of scurvy. Any other use of vitamin C in man lacks controlled experimental justification.

The addition of vitamin D to a diet rachitogenic but otherwise adequate, raised the resistance of rats to a "rat typhoid" infection fed by mouth in

an experiment by Robertson and Ross.[77] Greene[37] showed that more susceptibility to intranasal inoculation with *B. lepisepticum* was present in vitamin D-deficient rabbits, and a higher morbidity and mortality following intranasal inoculation with Type 1 pneumococcus than controls. Nonetheless, from these beginnings which, as has been pointed out, are in many respects tenuous or at least "highly experimental," the idea of vitamin deficiency is at the back of many of our troubles with infectious disease.

Factors that have contributed to the expansion of this idea are undoubtedly in the first place, the elucidation of vitamin deficiency as the cause of a number of non-infectious diseases: rickets, scurvy, beri-beri, and pellagra; and second, advancement in knowledge of the chemical nature of vitamins which has made possible their production and sale in seemingly unlimited quantity.

It should be noted here that all the non-infectious diseases due to vitamin deficiencies, when viewed epidemiologically, follow limited patterns of distribution which in themselves bespeak vitamin deficiency, and show a complete correspondence with demonstrated patterns of vitamin deficiency. Nevertheless, the lack of association between the distribution of any of the infectious diseases and known vitamin deficiency has not seemed to interfere in the least with generalizations drawn almost exclusively from laboratory experiments in which animals subjected to the severest vitamin deficiencies have been shown to vary in their resistance to infection. Watson[107] summed up the situation briefly, "The available evidence, taken as a whole, would seem to suggest that vitamins B and D have little, if any influence on resistance, while in the case of vitamin C, the observations recorded are particularly confusing and difficult to interpret."

Another factor that adds to the confusion is the interpretation of reported favorable therapeutic effects of various vitamins in a number of infectious diseases as an indication that the converse—vitamin deficiency—was responsible for the disease.

For example, good results from vitamin A therapy in treatment of measles were reported by Ellison.[25] He divided 600 cases of measles into 2 equal groups, one of which received the regular diet supplied to measles cases and cod-liver oil during convalescence, and the other received as supplement from the day of admission a concentrate containing 300 Carr and Price units of vitamin A and 2000 international units of vitamin D, the equivalent of approximately 1 oz. high grade cod-liver oil. This supplementary vitamin was continued for from 7 days to 3 weeks. He found that, of the treated 300 cases, there were 11 deaths (3.7%), and of the untreated cases there were 26 deaths (8.7%), a difference of 2.5 times the standard error, or 3.7 times the probable error. On the other hand, Mackay[55] and associates found no favorable results in studies apparently better controlled.

Sutliff, Place and Segool[92] treated a series of 509 cases of scarlet fever for 10 days after admission with a total of 400,000 U.S.P. units of vitamin A. The incidence of otitis media in this series was 9.4% as compared to 11.3% in 343 cases which were not treated with cod-liver oil. They found its prophylactic use apparently was without effect on the liability of scarlet fever patients, none of whom suffered from clinical deficiencies, to develop otitis media. Clausen[15] agreed with the idea that there was no obvious benefit from administration of carotene during scarlet fever and

was inclined to think that his cases did not suffer from a deficiency of vitamin A so no benefit should have been expected.

The effect of vitamin A on the course or incidence of other infections in man has been investigated, but vitamin-A deficiency was not shown before the studies began. Donaldson and Tasker[23] believed that a favorable effect on the outcome in pneumonia was obtained from the administration of vitamin A. Orenstein,[68] however, in the treatment of pneumonia in South African native mine employees, found that 375 cases treated with vitamin A and 389 cases acting as controls had almost identical case mortality, complications, lung involvement, and so on. He reported no benefit from this type of therapy.

The expansion of the idea of vitamin deficiency and susceptibility to infection has now extended into the realm of general popularity. In spite of the fact that the adequacy of the use of natural foods rather than vitamin pills and capsules have been repeatedly stressed by nutritionists, the drug store, rather than the grocery store, has become the dispensary for vitamin preparations in all sorts of combinations recommended for perhaps chiefly the prevention of the common cold, and now, in view of the stress on keeping fit during the emergency, for the maintenance of defense work at highest pitch.

The high pitch of vitamin popularity is well portrayed by an article in the section on Medicine and the War under the title, "Nation Faces Vitamin A Deficit."[67] In this item the Fish and Wildlife Service of the Department of the Interior recently warned that the nation faces a vitamin A deficit, that the chief source of vitamin A in the United States, the soupfin shark fishery, apparently is being rapidly depleted. It was pointed out that landings in February, 1944 were 70% below those of February, 1943, although fishermen had intensified their efforts. At the center of the fishery, landings for February, 1944 were about one-third those of the corresponding month of 1943. The Fish and Wildlife Service announced that vitamin A stock held by producers and pharmaceutical houses at the end of February, 1944 totaled approximately 51 trillion units as compared to 88 trillion units at the end of February, 1943. They stated that indications are that consumption of vitamin A in the United States now exceeds production.

Two major factors working in combination seem to have contributed to the wholesale consumption of supplementary vitamins which has outdistanced the development of any scientific basis for their use. One of these has been the development of knowledge of the chemical nature of vitamins, which has made possible their manufacture and sale direct to the public through modern advertising. For instance, at a drug store counter recently, a person whose general appearance indicated an economic and intelligence status which made one feel that she needed a good selection of food, was heard to ask for a particular pharmaceutical preparation containing so many units of this and that vitamin with addition of one or two of the other vitamins, using their correct chemical names—all in terms which compared favorably with those used by the most elaborate prescription writer in the days when materia medica was a pivot on which Medicine revolved.

The other has been the tendency of medicine itself to "try" this new line of pharmaceuticals for the many conditions encountered for which it has no satisfactory remedy.

Vitamin Deficiency and Virus Infections. Attempts to show that certain vitamins increase resistance of the animal to various virus infections

have generally been completely unsuccessful. In several instances it has been shown that susceptibility to these infections actually has been decreased. This resistance to virus disease might be said to have been noted indirectly by Underwood[103] as early as 1789 when he observed that poliomyelitis attacked the finest children. In Rous's[80] work, fowls sick from an intercurrent disease, characterized by rhinitis, conjunctivitis and marked depression and emaciation, were less susceptible to the sarcoma virus than healthy ones. The sarcoma nodule may cease to grow and even regress during the period of illness in the host, and with return of health the tumor may reappear and grow.

Marsh-Buffalo mice inoculated with sarcoma 180 were maintained on a synthetic diet containing vitamins of the B group except B_6.[5] The rate of tumor growth showed a marked and significant drop when B_6 was deficient. When vitamin B_6 was added to the diet without other change or increase in the caloric content, the rate of tumor growth increased. There was increased rate of growth on a diet completely deficient in B complex but with vitamin B_6 added. Pantothenic acid deficiency had no effect on the rate of tumor growth in these experiments.

Underfeeding appeared to affect the initiation and growth of tumors differently.[93] Fewer tumors were formed in underfed mice and they were initiated at a later time. The rate of growth was about the same in underfed as in full-fed animals. When previously full-fed animals were subsequently underfed, the rate of growth of the tumors diminished. In determining the cause of retardation of initiation and growth of tumors, the possibility of restricted metabolism and growth of the animals, whether produced by underfeeding or an interference with utilization, must be considered.

When rabbits were deprived of food and injected with vaccinia, the lesions were fewer or smaller. If the animals were allowed to drink water, thus increasing the amount of interstitial fluid, the lesions were even fewer. The lesions were more numerous if the interstitial tissues were dehydrated.[91]

In experiments by Langenbeck and Enderling[52] with foot-and-mouth virus, no protection was reported from vitamins A, B_1, B_2, C, or D in the guinea pig.

Cowdry, Lucas, and Neff[18] in experiments with a total of 70 B_1-deficient and 43 B_2-deficient rats found that the rats deficient in these vitamins showed slightly more deaths than do normal rats when injected intracerebrally with herpes virus. They did not consider the evidence sufficient to show that resistance to herpes was actually reduced by these deficiencies.

Jungeblut[50] reported a definite decrease in the percentage of animals developing paralysis when natural vitamin C therapy was used in experimental poliomyelitis. Sabin[81] found no difference in the appearance of paralysis in monkeys deficient in vitamin C as compared to those who had had adequate amounts. The number of experimental animals was small: only 12 animals out of 25 survived the preliminary vitamin C-deficient diet and could be used for the poliomyelitis experiment. There were 20 control animals on an adequate vitamin C diet. Of the total number—32—all but one developed paralysis; the one was in the untreated deficient control group.

Foster and associates,[28,29,30,31] in experiments with mice on different levels of thiamin intake, reported the incidence of paralysis in mice injected with murine poliomyelitis virus (Lansing strain) on the high-thiamin diet to be several times that in mice on the thiamin-deficient diet.

In the average of their first 3 experiments, totaling 646 mice, mice on the low-thiamin diet had 13% paralysis as compared to 74% in mice on the high-thiamin diet. In a fourth experiment, the low-thiamin mice were given a maintenance level of thiamin, about 40% of the intake of the normally fed mice, to prevent their dying of deficiency for at least 21 days after inoculation, in which time paralysis would be most likely to develop. The low-thiamin group showed no increase in mortality as compared to the high-thiamin group. The incidence of paralysis in mice on the high-thiamin diet was several times that in the low-thiamin group, and paralysis was followed by death in a few days. The same workers made the interesting observation that a similar reduction in incidence of paralysis was produced by simple restriction of the stock diet; by restricting carbohydrate intake, paralysis and death were delayed.

A group of 35 mice on a thiamin-deficient diet and a group of controls at an optimum level were inoculated intracerebrally with Lansing mouse passage poliomyelitis virus in experiments by Rasmussen and associates.[74] None of the mice in the thiamin-deficient group showed paralytic symptoms by the 14th day, while 25 of the 35 mice on the optimal diet had developed paralysis. Inoculations with Theiler's virus were performed on mice in a similar experiment by these workers with riboflavin. Nine of the 26 in the deficient group developed paralysis, as compared to 16 out of 26 on an optimal amount and 15 out of 27 on a high-riboflavin allowance.

Ward, Sabin, Najjar, and Holt[105] found that children with paralytic poliomyelitis gave essentially the same results in thiamin excretion tests as those in normal children, suggesting that thiamin may not be a factor in determining whether paralysis will develop.

Toomey[94] reported experimental evidence that the ingestion of vitamin D protected monkeys from poliomyelitis when the virus is later given by way of the gastro-intestinal tract, and that the vitamin D-deficient animals were more susceptible to the disease when given by this route. He also presented evidence that the virus of poliomyelitis will spread along the nerves of vitamin D-deficient monkeys if virus is placed in contact with postganglionic fibers; poliomyelitis virus does not spread along the well-medullated nerves of healthy monkeys.[95] Results of studies by Sabin and associates[82] were non-confirmative of Toomey's conclusions, and they found no evidence that the capacity of poliomyelitis virus to invade the central nervous system along peripheral nerves depended on vitamin A deficiency. Freshly passaged virus was used in Sabin's experiments and glycerinated M.V. in Toomey's work; the lower concentration of virus probably was a factor in the latter's experiments.

Cottingham and Mills[17] have shown that vitamin deficiency severe enough to retard growth produces a corresponding reduction in phagocytic activity. In their work, the greatest phagocytic activity seemed to occur at levels of vitamin intake higher than those needed for good growth. They pointed out and emphasized[64] that low phagocytic activity was present with moderate vitamin deficiency, but it rose to normal when vitamin deficiency was severe. The work of Gellhorn and Dunn[33] seemed to bear out their results.

The Common Cold. Reports of experimental work on vitamin A and its effect on illness, especially colds, are conflicting. Most of the studies show that the incidence of colds was less, but controls generally were inadequate and volunteers were usually selected for the experiments.

The subjective element was eliminated in Cameron's[13] study by giving the controls a placebo. The daily intake of vitamin A was calculated for

her subjects also. In this experiment the duration of colds was decreased by adding 5000 i. u. of vitamin A to a diet already containing 4300 i. u. daily, but the incidence of colds was not decreased.

Clausen[14,15] discussed the limits of the anti-infective value of provitamin A or carotene. From studies of the carotinoid pigment of the blood plasma in 1322 children after 2 years of age, he concluded that they generally received a diet adequate in vitamin A. Evidence that low intake of carotene was responsible for recurrent respiratory infections was not obtained. In his opinion, probably not more than 5 to 10% of these respiratory infections could be attributed to lack of carotene.

In several often-quoted experiments on human subjects, contradictory and rather questionable results were obtained. One group of young adult students were selected at random. They were divided into 3 groups: one received 200,000 i. u. vitamin A and 400 u. vitamin D per week; another received 400 u. vitamin D as viosterol; and the third group received maize oil. They were observed for over a year without evidence that supplemental vitamin A reduced the incidence of colds and without a significant difference in the frequency of other respiratory infections. Winter colds apparently were several days shorter when extra vitamin A was given.[84]

Another investigation in 4 groups varying in size from 6 to 94 infants who were given small, moderate, large, and maximum amounts of vitamin A were observed for from 4 to 12 months without showing any significant difference in the incidence or severity of respiratory infections. The group receiving the largest amount of vitamin A had no more protection against respiratory infections than any of the other groups.[2]

Administration of vitamin A in the form of haliver oil or high-vitamin A foods to 50 school children divided into 2 groups and paired by age, sex, nutrition and history of susceptibility to colds showed a decrease in the incidence and severity of colds compared to a group of 25 control children who had a history of high resistance to colds. Improvement in the general health as shown by an increase in weight accompanied this increased resistance to colds. The results of this experiment are hardly conclusive, since there was involuntary selection for the various groups, as susceptible children were put into the groups to be given supplement, and other factors such as the general diets and intake of other food essentials were not considered.[32]

In 162 medical students examined by Jeghers,[49] over one-third had low photometer readings and 12% had clinical manifestations of vitamin A deficiency. The incidence of colds in the subnormal group was approximately the same as that of the normal students, but they apparently were of longer duration.

Several other workers haye carried out experiments on small groups of individuals in an attempt to show that vitamin A, in particular, is efficacious in preventing colds. Winholt and Jordan[112] showed little correlation in types of infant feeding and colds. Those with colds had a number of ailments other than colds, few of which illnesses were of infectious origin. Cramer[19] refers to Dr. Curry Mann's report that boys supplied with an extra milk ration in a boys' school had an improvement in gains in weight and height and general health, and a "complete absence of illness." Wright, Frosst, Richel, and Lawrence[117] gave 20 infants large amounts of vitamin A over a period of months, and as controls had 40 infants under the same conditions but given the amount of vitamin A

usually supplied in the group. No appreciable difference in the incidence of upper respiratory infections was found in the two groups.

Cod-liver oil supplied to workers in industry was reported to reduce colds, lost time, and hours of absence by Holmes, Pigott, Sawyer and Comstock.[47] One tablespoonful cod-liver oil daily was given to 185 from December to March inclusive, and 128 were used as controls. Of the workers receiving cod-liver oil, no colds developed in 55.1%, as against 32.8% in the controls. The cod-liver oil group lost time was reduced 51.9%, as compared to 40.6% in the controls. The average hours of absence were reduced from 20.4 in 1930 to 12.8 in 1931 in the cod-liver oil group, and in the controls increased from 17.4 to 25.1. Workers comparable in age, weight, sex, and type of work were selected for this experiment, but no control or record was made of the diet before or during the experiment.

Hess, Lewis and Barenberg[43] found no difference in the frequency of colds or the prevention of pneumonia and otitis media in 40 infants given large amounts of carotene daily, 40 given large amounts of haliver oil, and 80 no vitamin A supplement; all received viosterol. Infections of the skin, as impetigo, were present in the vitamin groups as often as in the control group.

The effect of vitamins on respiratory infections in infants was summed up by Hess.[42] Vitamins A and D are not effective in increasing immunity to respiratory infection, while a lack of vitamin C may cause heightened susceptibility to infection of the respiratory tract.

In Beard's[4] study, 36 first-year medical students were given cod-liver oil concentrate tablets daily and the incidence and severity of colds were recorded; 58.3% showed a definite prophylactic effect compared to their colds in the previous year as determined from memory, 11.1% a slight prophylactic effect, and 30.6% no effect. During an influenza epidemic at the time, 56% were attacked, approximately the same percentage that occurred in students not receiving cod-liver oil. In Tress'[99] paper a comparison was made between the incidence of colds in a test year and the year before. Two hundred and twenty-five children took halibut-liver oil regularly or irregularly. Of the ones taking it regularly, 78% had fewer attacks. In a group of 76 children receiving cod-liver oil, 75% of those taking it regularly had fewer colds.

Hoelzel[46] saw a parallelism between the incidence of colds and nutritional hydration from his personal experience. During fasting or marked undernutrition colds did not develop, but appeared after periods when edema especially due to protein starvation was prominent. Keeping the hydration of the organism at a relatively low level, mainly by restricting carbohydrates and maintaining an adequate protein level may have prevented some colds. After excessive secretions were formed, bacteria then may have complicated the condition.

Summary. "Few investigators doubt that severe deficiency of vitamin A, or any vitamin, will lower resistance to infection, and almost all will agree that administration of vitamin A during the course of any infection will have little beneficial effect on the outcome unless a deficiency is present. Some workers believe that the frequency and high mortality rate in pneumonia of infants who are deficient in vitamin A result from a disturbance of function of the mucosa of all parts of the lungs. Others believe that administration of vitamin A in large amounts is beneficial in preventing common infections of the respiratory tract. This subject, however, is in general extremely controversial. Enough evidence

indicates that there are many other factors of equal or greater influence in infection than vitamin A and that there is no justification for calling vitamin A the 'anti-infection' vitamin."[39]

In view of such a typical confusing statement, in a handbook of nutrition it should be pointed out that the science of nutrition itself (and science tends to be enthusiastic about its own wares) has by no means been responsible for the present state of affairs. McCollum, the dean of nutritionists, himself under such titles as "Common Sense and Nutrition" and "What is the Right Diet?" has continually stressed the importance of the right food rather than supplementary vitamins. He[59] brought out the fact that vitamin A is anti-infective merely in the sense that it prevents the typical keratinization of tissues produced by avitaminosis A and that it does not affect general immunity. He stated that from experiments there is no basis for the belief that vitamin A is clinically effective in infections caused by specific pathogenic organisms or in infectious disease unassociated with characteristic structural breakdown of epithelial tissue and the accompanying localized infection typical of vitamin A deficiency.

Wolbach early pointed out that the essential lesion in what has been made the classic example of vitamin deficiency and susceptibility to infection was not infection, but only keratinized epithelium which merely resembled pus, and infection was secondary.

Harris, Innes and Griffin[41] emphasized that the existing data afforded no basis for the belief that vitamin A therapy is likely to be effective in combatting acute general infections due to specific pathogens or in infectious diseases or toxemias unassociated with the changes in epithelial tissue and localized infection characteristic of vitamin A deficiency.

Hess, Lewis and Barenberg[43] concluded that our dietary is not deficient in vitamin A, and a lack is present generally only as a result of such circumstances as poor selection of diet or defective absorption.

Studying the vitamin A reserve in over 300 specimens of human liver, Moore[65] found a wide variation in the amount present with adequate amounts in a wide variety of infective conditions. He qualified the term "anti-infection" as being justifiable only in a sense complementary to the idea that a deficiency of vitamin A leads to lowered resistance.

Although the mass of evidence is to the effect that susceptibility to a number of experimental infections can be influenced by drastic deprivation of vitamins, it is quite impossible to interpret the mass, or perhaps better, the maze of experimental evidence on vitamin deficiency and susceptibility to infection further than to point out that the premises which originally formed the basis of the idea are by no means sufficient to substantiate vitamin deficiency as an important principle in epidemiology.

In the first line of evidence, famine and pestilence, it is by no means clear that the nutritional deficiency itself makes for the occurrence of infectious disease through any lowering of resistance to infection. It would appear, rather, that pestilence following famine can usually be accounted for more properly as a secondary result of famine due to such factors as an accompanying breakdown in sanitation. This is not to say that disease, having developed, may not run a more severe course or be more highly fatal in nutritionally deficient people.

In the second of these lines, xerophthalmia, the idea of increased susceptibility to infection as such appears to be only in part correct. In the first place, aggregation of keratinized epithelial tissue, mistakenly called pus, appears to account for the emphasis on increased susceptibility; and in the second place, the infections which do occur in these cases are not

systemic epidemic infectious disease, but, rather, local tissue infections which find suitable soil in keratinized epithelium, and hence to be regarded as entirely secondary. Finally, this disease—the nearest approach we have to a nutritional deficiency as an epidemiologic determinant in infectious disease—is of extremely limited distribution, and in a pattern which can be accounted for on the basis of nutritional deficiency occurring in the same pattern. The distribution of disease always reflects its epidemiology. So far, in spite of numerous hypotheses which have been advanced so largely from "highly experimental findings," one cannot point to a single epidemic disease which exhibits any distributional feature clearly or even partially corresponding to those of any known or even suspected nutritional deficiency. Nonetheless, from a few slender threads of fact, the supplementing of a dietary from the grocery store admittedly containing all the vitamins necessary to health (even though all may not, either by reason of incorrect selection, processing or cooking, or for economic reasons obtain a good dietary) by comparatively enormously more expensive drug store vitamins taken largely to ward off infections, has grown into one of the nation's major commercial industries.

It has now reached the point, for example, where a falling off in the catch of soupfin sharks—an only recently added source of vitamin A—is viewed with alarm as an impending national calamity.

Perhaps the recent experimental demonstration—even more clear-cut than any of the experimental evidence to the contrary—that vitamin-deficient animals are actually *less* susceptible to a number of virus infections (and these account for the majority of our infectious disease) will serve to call a halt on what appears to be a needless and expensive and therefore inadequate way of insuring a "balanced diet" to our population.

This review prompts the formulation of the proposition that vitamin deficiency as a factor in susceptibility to infection is not a general epidemiologic principle. The indications are that only deficiencies of certain vitamins affect susceptibility to certain types of infections and that these occur only in limited areas where these vitamin deficiencies reach a sufficiently severe degree to produce tissue changes which are favorable sites for secondary infection.

REFERENCES

(1.) **Badger, L. F., Masunaga, E.,** and **Wolf, D.**: Pub. Health Rep., **55**, 1027, 1940. (2.) **Barenberg, L. H.,** and **Lewis, J. M.**: J. Am. Med. Assn., **98**, 199, 1932. (3.) **Bateman** (quoted by **Hirsch**): vol. 1, p. 579. (4.) **Beard, H. H.**: J. Am. Dietet. Assn., **10**, 193, 1934. (5.) **Bischoff, F., Ingraham, L. P.,** and **Rupp, J. J.**: Arch. Path., **35**, 713, 1943. (6.) **Blackfan, K. D.,** and **Wolbach, S. B.**: J. Pediat., **3**, 679, 1933. (7.) **Blegvad, O.** (quoted by **Widmark, E.**): Lancet, **1**, 1206, 1924. (8.) **Bloch, C. E.**: Jahrb. f. Kinderh., **89**, 405, 1919. (9.) **Bloch, C. E.**: Am. J. Dis. Child., **28**, 659, 1924. (10.) **Bloch, C. E.**: Acta pædiat., Suppl. 2 (Lecture, 14th Scandinavian Pædriatric Congress), **1**, 61, 1928. (11.) **Bloomfield, A. L.,** and **Lew, W.**: J. Nutr., **25**, 427, 1943. (12.) **Boynton, L. C.,** and **Bradford, W. L.**: J. Nutr., **4**, 323, 1931.

(13.) **Cameron, H. C.**: J. Am. Dietet. Assn., **11**, 189, 1935. (14.) **Clausen, S. W.**: J. Am. Med. Assn., **101**, 1384, 1933. (15.) **Clausen, S. W.**: New York State J. Med., **34**, 154, 1934. (16.) **Corrigan** (quoted by **Hirsch**). (17.) **Cottingham, E.,** and **Mills, C. A.**: J. Immunol., **47**, 493, 1943. (18.) **Cowdry, E. N., Lucas, A. M.,** and **Neff, C. F.**: J. Infect. Dis., **57**, 174, 1935. (19.) **Cramer, W.**: Lancet, **2**, 774, 1927. (20.) **Cramer, W.,** and **Kingsbury, A. N.**: Brit. J. Exp. Path., **5**, 300, 1924.

(21.) **Daniels, A. L., Armstrong, M. E.,** and **Hutton, M. K.**: J. Am. Med. Assn., **81**, 828, 1923. (22.) Dietary Deficiency and Poliomyelitis, J. Am. Med. Assn., **124**, 986, 1944. (23.) **Donaldson, S.,** and **Tasker, J.**: (Quoted from the Vitamins, 1939.) (24.) **Drummond, J. C., Baker, A. L., Wright, M. D., Marrian, P. M.,** and **Singer, E. M.**: J. Hyg., **38**, 356, 1938.

(25.) **Ellison, J. B.**: Brit. Med. J., **2**, 708, 1932. (26.) **Emmett, A. D.**: Science, **52**, 157, 1920.

(27.) **Findlay, G. M.**: J. Path. and Bact., **26**, 1, 1923. (28.) **Foster, C., Jones, J. H., Henle, W.,** and **Dorfman, F.**: Proc. Soc. Exp. Biol. and Med., **51**, 215, 1942. (29.) **Foster, C., Jones, J. H., Henle, W.,** and **Dorfman, F.**: Science, **97**, 207, 1943. (30.) **Foster, C., Jones, J. H., Henle, W.,** and **Dorfman, F.**: Am. J. Med. Sci., **205**, 465, 1943. (31.) **Foster, C., Jones, J. H., Henle, W.,** and **Dorfman, F.**: J. Exp. Med., **79**, 221, 1944.

(32.) **Gardner, E. L.,** and **Gardner, F. W.**: Am. J. Dis. Child., **47**, 1261, 1934. (33.) **Gellhorn, E.,** and **Dunn, J. O.**: J. Nutr., **13**, 317, 1937. (34.) **Goldblatt, H.,** and **Benichek, M.**: J. Exp. Med., **46**, 699, 1927. (35.) **Green, H. N.,** and **Mellanby, E.**: Brit. Med. J., **2**, 691, 1928. (36.) **Green, H. N., Pindar, D., Davis, G.,** and **Mellanby, E.**: Brit. Med. J., **2**, 595, 1931. (37.) **Greene, M. R.**: Am. J. Hyg., **17**, 60, 1933. (38.) **Gross, L.**: J. Path. and Bact., **27**, 27, 1924.

(39.) Handbook of Nutrition, Chicago, Am. Med. Assn., 1943. (40.) **Harris, L. J.**: Vitamins in Theory and Practice, New York, MacMillan, 1935. (41.) **Harris, L. J., Innes, J. R. M.,** and **Griffin, A. S.**: Lancet, **2**, 614, 1932. (42.) **Hess, A. F.**: New England J. Med., **207**, 637, 1932. (43.) **Hess, A. F., Lewis, J. M.,** and **Barenberg, L. H.**: J. Am. Med. Assn., **101**, 657, 1933. (44.) **Hess, A. F., McCann, G. F.,** and **Pappenheimer, A. M.**: J. Biol. Chem., **47**, 395, 1921. (45.) **Hirsch, A.**: Handbook of Geographical and Historical Pathology. Vol. I. Acute Infective Diseases (trans. by Creighton, C.), London, New Sydenham Society, p. 545, 1885. (46.) **Hoelzel, F.**: Proc. Soc. Exp. Biol. and Med., **25**, 454, 1928. (47.) **Holmes, A. D., Pigott, M. G., Sawyer, W. A., and Comstock, L.**: J. Ind. Eng. Chem., **24**, 1058, 1932. (48.) **Hou, H. C.**: Chinese Med. J., **53**, 47, 1938.

(49.) **Jeghers, H.**: J. Am. Med. Assn., **109**, 756, 1937. (50.) **Jungeblut, C. W.**: J. Exp. Med., **66**, 459, 1937.

(51.) **Kuttner, A. G.**: J. Clin. Invest., **19**, 809, 1940.

(52.) **Langenbeck, W.,** and **Enderling, A.**: Zentralbl. f. Bakt., **140**, 112, 1937. (53.) **Laqueur, E., Wolff, L. K.,** and **Dingemanse, E.**: Deutsch. med. Wchnschr., **54**, 1495, 1928. (54.) **Lassen, H. C. A.**: J. Hyg., **30**, 300, 1930.

(55.) **Mackay, H. M. M., Linford, H. M., Mitman, M.,** and **Wild, M. H.**: Arch. Dis. Child., **11**, 127, 1936. (56.) **Macy, I. G.,** and **Outhouse, J.**: Am. J. Dis. Child., **37**, 379, 1929. (57.) **McClung, L. S.,** and **Winters, J. C.**: J. Infect. Dis., **51**, 469, 1932. (58.) **McCollum, E. V.**: J. Am. Med. Assn., **68**, 1379, 1917. (59.) **McCollum, E. V. Orent-Keiles, E.,** and **Day, H. G.**: The Newer Knowledge of Nutrition, New York, Macmillan, p. 324, 1939. (60.) **McCoord, A. B.,** and **Clausen, S. W.**: Unpublished data, referred to in "The Vitamins," p. 80, 1939. (61.) **McCullough, N. B.**: J. Infect. Dis., **63**, 34, 1938. (62.) **Mellanby, E.**: Brit. Med. J., **1**, 515, 1926. (63.) **Mellanby, E.,** and **Green, H. N.**: Brit. Med. J., **1**, 984, 1929. (64.) **Mills, C. A.,** and **Cottingham, E.**: J. Am. Med. Assn., **125**, 229, 1944. (65.) **Moore, T.**: Lancet, **2**, 669, 1932. (66.) **Mori, S.**: Bull. Johns Hopkins Hosp., **33**, 357, 1922.

(67.) Nation Faces Vitamin A Deficit, J. Am. Med. Assn., **125**, 39, 1944.

(68.) **Orenstein, A. J.**: South Africa Med. J., **6**, 685, 1932. (69.) **Osborne, T. B.,** and **Mendel, L. B.**: J. Am. Med. Assn., **76**, 905, 1921.

(70.) **Pemberton, H.,** and **Bessey, O. A.**: Science, **89**, 368, 1939. (71.) **Pijoan, M.,** and **Lozner, E. L.**: New England J. Med., **231**, 14, 1944. (72.) **Pijoan, M.,** and **Sedlacek, B.**: Am. Rev. Tuberc., **48**, 342, 1943. (73.) **Pritchett, I. W.**: J. Exp. Med., **46**, 557, 1927.

(74.) **Rasmussen, A. F., Waismann, H. A., Elvehjem, C. A.,** and **Clark, P. F.**: J. Bact., **45**, 85, 1943. (75.) **Rinehart, J. F.**: Internat. Clin., **2**, 22, 1937. (76.) **Rinehart, J. F., Connor, C. L.,** and **Mettier, S. R.**: J. Exp. Med., **59**, 97, 1934. (77.) **Robertson, E. C.,** and **Ross, J. R.**: J. Pediat., **1**, 69, 1932. (78.) **Rose, S. B.,** and **Rose, W. B.**: J. Infect. Dis., **59**, 174, 1936. (79.) **Ross, J. R.,** and **Robertson, E. C.**: Am. J. Dis. Child., **43**, 547, 1932. (80.) **Rous, P.**: J. Exp. Med., **13**, 397, 1911.

(81.) **Sabin, A. B.**: J. Exp. Med., **69**, 507, 1939. (82.) **Sabin, A. B., Ward, R., Rapoport, S.,** and **Guest, G. M.**: Proc. Soc. Exp. Biol. and Med., **48**, 451, 1941. (83.) **Sherman, H. C.,** and **Burtis, M. P.**: Proc. Soc. Exp. Biol. and Med., **25**, 649, 1928. (84.) **Shibley, G. S.,** and **Spies, T. D.**: J. Am. Med. Assn., **103**, 2021, 1934. (85.) **Shurley, B. R.,** and **Turner, R. G.**: J. Am. Med. Assn., **94**, 539, 1930. (86.) **Sigerist, H. E.**: Civilization and Disease, Cornell Univ. Press, 1943. (87.) **Simmonds, N.**: J. Am. Med. Assn., **111**, 1073, 1938. (88.) **Smith, T.**: J. Med. Res., **29**, 291, 1913. (89.) **Spence, J. C.**: Acta pædiat. (Trans. Second Int'l Ped. Congress, Stockholm, Sweden), **11**, 541, 1930. (90.) **Spindler, L. A.**: J. Parasitol., **20**, 72, 1933. (91.) **Sprunt, D. H.**: J. Exp. Med., **75**, 297, 1942. (92.) **Sutliff, W. D., Place, E. H.,** and **Segool, S. H.**: J. Am. Med. Assn., **100**, 725, 1933.

(93.) **Tannenbaum, A.**: Am. J. Cancer, **38**, 335, 1940. (94.) **Toomey, J. A.**: Am. J. Dis. Child., **53**, 1202, 1937. (95.) **Toomey, J. A.**: Am. J. Dis. Child., **60**, 548, 1940. (96.) **Topley, W. W. C., Greenwood, M.,** and **Wilson, J.**: J. Path. and Bact., **34**,

163, 1931. (97.) **Torrance, C. C.**: Am. J. Hyg., **18**, 375, 1933. (98.) **Torrance, C. C.**: Am. J. Hyg., **23**, 74, 1936. (99.) **Tress, E. M.**: Am. J. Digest. Dis. and Nutr., **1**, 795, 1939. (100.) **Turner, R. G.**: Proc. Soc. Exp. Biol. and Med., **26**, 233, 1928. (101.) **Turner, R. G., Anderson, D. E.**, and **Loew, E. R.**: J. Infect. Dis., **46**, 328, 1930. (102.) **Tyson, M. D.**, and **Smith, A. H.**: Am. J. Path., **5**, 57, 1929.

(103.) **Underwood, M.**: A Treatise on the Diseases of Children, With General Directions for the Management of Infants From Birth, 4th ed., London, Mathews, 1799.

(104.) The Vitamins, Chicago, Am. Med. Assn., 1939.

(105.) **Ward, R., Sabin, A. B., Najjar, V. A.**, and **Holt, L. E., Jr.**: J. Bact., **45**, 86, 1943. (106.) **Watt, J. Y. C.**: Am. J. Hyg., **39**, 145, 1944. (107.) **Watson, M.**: J. Hygiene, **37**, 420, 1937. (108.) **Webster, L. T.**: J. Exp. Med., **52**, 931, 1930. (109.) **Webster, L. T.**, and **Pritchett, I. W.**: J. Exp. Med., **40**, 397, 1924. (110.) **Werkman, C. H.**: J. Infect. Dis., **32**, 255, 1923. (111.) **Werkman, C. H., Nelson, V. E.**, and **Fulmer, E. I.**: J. Infect. Dis., **34**, 447, 1924. (112.) **Winholt, W. F.**, and **Jordan, E. O.**: J. Am. Med. Assn., **81**, 280, 1923. (113.) **Wolbach, S. B.**, and **Howe, P. R.**: J. Exp. Med., **42**, 753, 1925. (114.) **Wolff, L. K.**: Lancet, **2**, 617, 1932. (115.) **Wolford**: Famines of the World. (116.) **Wooley, J. G.**, and **Sebrell, W. H.**: Pub. Health Rep., **57**, 149, 1942. (117.) **Wright, H. P., Frosst, J. B., Richel, F.**, and **Lawrence, M. R.**: Canad. Med. Assn. J., **25**, 412, 1931.

(118.) **Zinsser, H., Castaneda, M. R.**, and **Seastone, C. V., Jr.**: J. Exp. Med., **53**, 333, 1931.

XUM

A CENTURY OF SUCCESSFUL PUBLICATION

The American Journal of the Medical Sciences desires to take this opportunity to congratulate the NEW ORLEANS MEDICAL AND SURGICAL JOURNAL, and DR. JOHN H. MUSSER, who has been its Editor for the last 17 years and was formerly editor of this journal, on the completion, last May, of its first 100 years of continuous publication. There are comparatively few medical journals that have survived such a long period of service. Among the existing journals in the English language, only four are able to point to such a record: The Edinburgh Medical and Surgical Journal (founded in 1805), the New England Journal of Medicine and Surgery (1812), The American Journal of the Medical Sciences (1820) and the Lancet (1825). The fact that the NEW ORLEANS MEDICAL AND SURGICAL JOURNAL has now entered this list of centenarians is evidence that, like its long-lived contemporaries, it has consistently maintained the highest possible standard of excellence and in so doing has been a powerful influence in the development of medical and scientific literature.

XUM

BOOK REVIEWS AND NOTICES

RORSCHACH'S TEST. 1. Basic Processes. By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago; Associate Professor of Psychology, Northwestern Univ. Foreword by WILLARD L. VALENTINE, PH.D., Head of Department of Psychology, Northwestern Univ. Pp. 223; 20 tables; 10 figs. New York: Grune & Stratton, 1944. Price, $3.50.

RORSCHACH'S ink-blot test cards provide a psychometric method whereby the subject's personality may be projected into a standardized environmental situation, thus offering a definite objective personality study. The author, who is less inclined to deviate from the teachings of the Master than are some others, has intended his book for the student and expert. Since he is not convinced that the group technique is of proven value, all responses were obtained from the individual; however, the use of group technique in the service will render its later evaluation possible. Rorschach's entire procedure includes scoring, tabulation of results and finally their interpretation. All of the subject's responses were written down *verbatim*, then "scored," *i. e.*, recorded in the accepted symbol language, but with no attempt at interpretation.

The author has employed some of the numerous Rorschach symbols, giving most space to the following: Z, the organization of activity, which in the main is concerned with the relations that one or more portions of the selection bear to each other; this part of the text is elucidated with 10 figures. M, the movement response, which represents the wish-fulfillment activities, similar to those in Freud's unconscious realm, and the dreamwork of other psychoanalysts. FV and Y, light determined response, response expressed by variations in light figure values. F+ and F− include the form quality evaluation; the + sign indicating the response is a common one, while − means the response is a new one. This experienced psychologist and ardent Rorschach research worker, has provided a book that is very trustworthy, and that uses caution in those problems that are definitely controversial. N. Y.

BABY DOCTOR. By ISAAC A. ABT, M.D. Pp. 308. New York and London: Whittlesey House, McGraw-Hill, 1944. Price, $2.50.

BABY DOCTOR may be described as a spirited anecdotal autobiography with an educational aim. It does more than portray the growth of a sagacious pediatrician-teacher from preliminary training to retirement age, though that tale is told richly with humor and good will. The book in addition is a résumé of the great progress attained by the new specialty of pediatrics during its first and fruitful half century. By the device of alternating amusing anecdotes with brief dissertations on medical problems, the author achieves an informatively charming personal history. I. W.

MANUAL OF UROLOGY. By R. M. LECOMTE, M.D., F.A.C.S., Professor of Urology, Georgetown Univ. Medical Department; Member of the American Urological Association. Third ed. Pp. 305; 60 figs. Baltimore: Williams and Wilkins, 1944. Price, $4.00.

THIS edition of a popular medical student's textbook continues to give "the beginner a groundwork of fundamentals on which to build a larger structure." A new section dealing with the innervation of the kidneys and pelvic viscera has been added. This includes several diagnoses and reviews the motor and

sensory pathways with particular reference to an interpretation of the mechanism of pain.

The discussion of the treatment of acute gonorrhea with sulfonamides is very brief, as is also the consideration of prophylaxis, so vital to our armed forces. On the whole, the subject matter is well proportioned and clearly presented. The light weight and dull finish of the paper is a boon to the reader. H. S.

THE WAR AND MENTAL HEALTH IN ENGLAND. By JAMES M. MACKINTOSH, M.D., Professor of Preventive Medicine, Univ. of Glasgow. Pp. 91. New York: Commonwealth Fund, 1944. Price, $.85.

DR. MACKINTOSH divides this thin volume of essays into 2 parts: the first group bearing the title "The Impact of War;" and the second, "Mobilization for Peace." The last 5 papers are of little general interest to the American reader since they deal for the most part with the difficulties which beset the various voluntary organizations which are concerned with mental health in Britain. The reader searches vainly for the connection with the "war" of Dr. Mackintosh's title. Even the section on rehabilitation does not mention the special and overwhelming problem of the mentally or physically disabled soldier. The first group of essays contains more valuable information.

Perhaps the best thing in the book is a letter which describes a rest center for bombed-out refugees. There is also a brief but excellent summary of the debit and credit of the government's evacuation of children. The author points out that careful planning is required to prevent maladjustment and heartbreak from marring the children's homecoming after the war. He impatiently dismisses the sentimental theory that "a thoroughly bad slum home in the city is better for a child than a good foster home in the country." Making smooth the return of children from a better to a worse environment will call for the concerted efforts of psychiatric social workers, child guidance clinics, and local health authorities. D. P.

THE WOUNDED GET BACK. By ALBERT Q. MAISEL. Foreword by Ross T. McINTIRE, Rear Admiral, Medical Corps, U.S.N., The Surgeon General of the Navy. Pp. 230. New York: Harcourt, Brace, 1944. Price, $2.50.

THE author, a correspondent granted special privileges by the Navy to inspect their hospital installations in the South Pacific, tells his story well. Though a layman, Maisel presents an account of military medical practice which will be of great interest to all physicians. Beginning with a description of the hospital ship Solace, the author discusses the base hospital in Auckland, the aërial evacuation of casualties by SCAT, the facilities at Guadalcanal and Tulagi, and includes an excellent discussion of the problem of malaria as met by our forces in these regions. Though dealing with a woeful subject, the author presents it in a manner so restrained, yet optimistic, that the book will be a source of comfort to all who have been left behind. H. S.

PERSISTENCE AND CHANGE IN PERSONALITY PATTERNS. By KATHERINE ELLIOTT ROBERTS and VIRGINIA VAN DYNE FLEMING. Monographs of the Society for Research in Child Development, Vol. VIII, No. 3 (Serial No. 36). Pp. 206; 26 tables. Washington, D. C.: National Research Council, 1943. Price, $1.50.

THIS Monograph reports a study of a group of women clients of the Advisory Service for College Women from the point of view of persistence and change in personality patterns. Traits such as self-confidence were traced through each client's life history to evaluate under what conditions they might persist or change. The studies are carefully made with the use of many psychologic evaluations and specific tests.

XUM

Life history material is difficult to study under any method of scientific research and the authors have been reluctant to present their findings as conclusions. They have produced supporting data for theories which have been well accepted by psychiatrists and social workers, and they point out the need for more scientific research. M. P.

ALLERGY IN PRACTICE. By SAMUEL M. FEINBERG, M.D., Associate Professor of Medicine and Chief of the Division of Allergy, Northwestern Univ. Medical School; President, American Association for The Study of Allergy, 1942–43. With the Collaboration of OREN C. DURHAM, Chief Botanist, Abbott Laboratories. Pp. 798; 36 figs. Chicago: Year Book Publ., 1944. Price, $8.00.

THE author presents a comprehensive and well-documented account of his subject. The first 4 chapters of the book deal with the general aspects of the problem of hypersensitivity in man. Then follows a detailed discussion of the different groups of allergens such as fungi, inhalants, foods, drugs and so forth. The 100 page chapter on pollens was written by Oren C. Durham. Numerous maps showing the distribution of many common plants as well as a brief consideration of the characteristic flora of each state should prove helpful to the physician.

The account of fungi as allergens is actually a short monograph on a subject in which the author has done much original work. He concludes "that airborne spores of common fungi constitute a major cause of allergic symptoms. The manifestations produced are mainly asthma and rhinitis." In view of the increasing interest in parasitic fungi, this indictment of the free living forms should be an added spur to the study of these plants, so long neglected by physicians.

Several chapters are devoted to the study of asthma and hay fever. The importance of contact dermatitis in wartime industry should have merited a more extensive discussion of this subject than it has received. Treatment is adequately dealt with. The author assumes that to treat the allergic patient it is first necessary to know something about the nature of allergy and the substances producing it. In supplying this information he succeeds very well. H. S.

CLINICAL UROLOGY. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., Director of Department of Urology (James Buchanan Brady Foundation) of the New York Hospital; and THOMAS KIRWIN, M.A., M.S., M.D., F.A.C.S., Attending Surgeon of Department of Urology (James Buchanan Brady Foundation) of the New York Hospital. Drawings by WILLIAM P. DIDUSEH. Second ed. Vols. 1 and 2. Pp. 1789; 220 figs.; 365 illus. Baltimore: Williams & Wilkins, 1944. Price, $10 set of 2 Vols.

THE first edition of this work, presented in 1940, was enthusiastically received as an authoritative and easily read treatise on urology. The many rapid advances in the urologic field have made necessary the presentation of a new edition. The stated purpose of the authors is to present "a practical survey of the nature, diagnosis, and treatment of anomalies and diseases of the genitourinary organs." According to the present stage of knowledge this purpose is accomplished. The volumes contain not only information on the urologic problems of the adult male, but also the problems concerning urology in women and children. It is written for the use of medical students, general practitioners, general surgeons, and urologists.

The first 5 chapters concern general diagnostic procedures; Chapter VI is on anesthesia; subsequent chapters take up the urogenital organs in anatomic sequence from without inward. For each organ there is a consideration of the embryology, anatomy, anomalies, physiology, injuries and diseases. Surgical and non-surgical therapy are discussed. The authors' methods of therapy

are emphasized, but they draw freely from the literature the opinions of other authorities.

New subjects presented in this edition are: the renal factor in hypertension, surgical treatment of arterial hypertension, calyceal resection, castration and hormonal treatment of carcinoma of the prostate, tidal drainage, continuous spinal anesthesia, dried blood plasma, new diets as related to urinary calculus, and methods of dissolving certain urinary calculi. New advances in chemotherapy as applied to gonorrhea, non-specific urinary infections, and pre- and postoperative treatment are thoroughly covered.

There is an extensive bibliography following each chapter. These comprehensive lists of references should be of great value to anyone desiring to go more deeply into any specialized subject.

From every angle this treatise is a most worth-while contribution to the urologic literature. L. La T.

THE ELECTROCARDIOGRAM. ITS INTERPRETATION AND CLINICAL APPLICATION. By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island and Harbor Hospitals; Formerly Instructor in Medicine, N. Y. Post Graduate Medical School, Columbia University. Pp. 403; 203 illus. and plates. New York: Grune & Stratton, 1944. Price, $7.50.

THIS book is definitely more than "just one more book on ECG." The spate of such publications has subsided in recent years, so that presentations of recent developments, such as the criteria for right versus left ventricular premature contractions, right versus left bundle branch block, signs of myocardial disease, chest leads, and the effects of coronary occlusion, etc., are conveniently found well considered in this up-to-date presentation. The underlying principles are covered briefly in the first 4 chapters. Here one regrets that more attention was not given to the ventricular layers with their autonomous vascular and conductive tissue connections. One misses, also, consideration of Wolferth's views (1942) on the distribution of potential, which are at variance with the electrical axis concept. In the clinical sections, a historical note, incidence, pathologic anatomy (miscalled "pathology"), and physiologic mechanisms are included for each condition, whenever pertinent. Full references are given at the end of each chapter, and the illustrations are numerous and adequate though they lack the uniformly technical excellence that we often find in books of this class; and the price is high.

The Author appears to have made good use of his acquaintance with ECG literature, and of a considerable personal experience, in this presentation. The possibilities and limitations of the method in the various diseased conditions of the myocardium, as well as in the arrhythmias, have obviously been carefully considered. E. K.

DER SCHWUND TUBERKULÖSER LUNGENKAVERNEN. By PROF. WALTER BERBLINGER, M.D. Pp. 130; 61 illus. Basel: Benno Schwabe, 1943. Price, 15 Swiss Fr.

THIS monograph deals with the processes involved in the healing and eradication of pulmonary tuberculous cavities. Berblinger reviews at considerable length the views of various pathologists relative to the possibility and mechanism of cavity eradication. It is noteworthy that Aschoff held that healing of tuberculous cavities was impossible without surgical intervention. The author reviews his experience with 32 cavities which had been under the suction treatment of Monaldi for periods up to 20 months. When their lungs were studied after the death of the patient, he could not establish a single case of cavity eradication. Prolonged drainage cleanses the cavity of its caseous contents, shrinks its walls, but never completely eradicates the specific tuberculous inflammatory changes in its walls. Though the sputum of such cases may become free of tubercle bacilli there is no certainty that,

XUM

with a change for the worse of the immunologic state of the patient, exacerbation may not take place. Only small elastic cavities can heal in such manner. Larger cavities, whether of the elastic or rigid wall type, can heal only by the occlusion of the exit bronchus or bronchi of the cavity which initiates the conversion of the cavity into a closed lesion. The author presents a detailed study of 9 cavities which had been observed by Roentgen ray during the life of the patients and were subsequently thoroughly investigated on the death of the individual. He comes to the conclusion that the factor of paramount importance in the healing of cavities is the permanent closing of the bronchi into which these cavities lead. He presents convincing evidence that the process begins as a tuberculous bronchitis which often originates at a considerable distance from the cavity. A non-specific inflammatory process then closes the bronchus beyond the tuberculous bronchitis and nearest the cavity. Once these bronchi are thoroughly closed, the bacilli in the cavity are deprived of oxygen and die off. The contents of the cavity become thickened by absorption of their moisture. The progression of the tuberculous process in the wall ceases and the inspissated contents are gradually absorbed by the surrounding tuberculous granulation tissue. He emphasizes that the outgoing bronchus is sealed before the cavity heals, for which he presents clear pathologic evidence. After the absorption of the caseous tissue from the center of the cavity the space is replaced by dense fibrous tissue. Often the wall of the exit bronchi becomes enmeshed in this scar which then has a characteristic appearance as given by the islands of cartilage that are seen in these scars.

This is a thorough, comprehensive though somewhat repetitious paper, and is of great value to all students of tuberculosis. M. L.

ONE HUNDRED YEARS OF AMERICAN PSYCHIATRY. Published for *The American Psychiatric Association*. By the following Contributors: HENRY ALDEN BUNKER, ALBERT DEUTSCH, J. K. HALL, SAMUEL W. HAMILTON, CLYDE KLUCKHOHN, WILLIAM MALAMUD, DOM THOMAS VERNER MOORE, WINFRED OVERHOLSER, RICHAR H. SHRYOCK, HENRY E. SIGERIST, EDWARD A. STRECKER, JOHN C. WHITEHORN, GREGORY ZILBOORG. Foreword by GREGORY ZILBOORG. Introduction by J. K. HALL. Pp. 649; 35 illus. New York: Columbia Univ. Press, 1944. Price, $6.00.

AMERICAN Psychiatry has indeed progressed far since the foundation of the American Psychiatry Association just 100 years ago, when lunatics were "put away" in an "insane asylum" for the protection of society and the convenience of relatives; and further still has it progressed since 100 years before that when lunatics were treated with whips and chains, as at the Pennsylvania Hospital (founded in 1751, the first in this country) to take philanthropic care of the sick and wounded. Yet, as Shryock here points out in the chapter on the Beginnings, brutality at that time was the rule—even the "relatively humane" Benjamin Rush advocated the "tranquilizer" and a whirling "gyrator" long after the gentle John Howard had done his work in England, and Pinel had struck off the chains from the insane at the Bicetre (1792).

In the handsome volume now before us, one gets a full view of 100 years of psychiatry in this country, from the descriptions of the mental hospitals, of psychiatric research and literature, psychiatric therapies, and especially of the American Psychiatric Association—which, known at first as the Association of Medical Superintendents of American Institutions for the Insane, celebrated its centenary at Philadelphia, its birthplace, last May. An authoritative, well documented production, the work is necessarily of interest chiefly to psychiatrists; however, Shryock's and Sigerist's opening chapters should have a much wider appeal, as should also such items as the fact that the American Psychiatric Association was the only national medical body in existence in this country 100 years ago, and that the American Journal of Insanity, just

3 months older than the Association, was the first periodical in English to be devoted to mental disease.

Psychiatry has become increasingly recognized by both medico and layman as one of the most important branches of medicine, to which fact this book amply testifies. The portrayal of the evolution of American psychiatry and its present trends and accomplishments is given in such detail that it is beyond the power of the Reviewer, not a psychiatrist himself, to evaluate. It should not seem altogether captious, however, to call attention to a frequently repeated criticism of psychiatry, namely, that in these days of medical objectivity, which gained momentum just about the time the American Psychiatric Association was being founded, psychiatry has lagged behind other medical disciplines in cultivating this quality. The nature of the human mind and its malfunctioning is, of course, chiefly responsible; but it is only since the last war that this lack of objectivity has been appreciated (Cp. Freud's lack of even statistical control of his psychoanalytic assertions). One wonders whether even today the average psychiatrist is sufficiently concerned about this shortcoming. Indeed, may not this be an important basis for the frequent criticism that in psychiatric studies "everyone has to start from scratch all over again." In the evaluation of psychiatric therapies, the empirical method still rules supreme; even in the recently introduced shock therapies we hear much about the comparative results of this or that form of shock or the best dosage in this or that condition, but painfully little that is objective as to why they are of use, or about the anatomical changes they produce. Such an uncertain basis may be of some use, but it is not the way that the nosology of internal diseases was established, that tuberculosis and other communicable diseases were conquered, or the efficiency of the sulphonamides and of penicillin proved. Could it be that another Weir Mitchell, as in 1894, is needed to jolt more of psychiatric research into objective lines? To be sure, Whitehorn's chapter on Psychiatric Research indicates that in certain centers there has been considerable research in recent years; yet the story of all phases of psychiatric research occupies but 27 of more than 600 pages of this book, and there is only one reference to work published before 1894 and only a dozen before the first World War.

The book is well presented and inexpensive for one of its size and quality. The illustrations also are good, though not too numerous and annoyingly separated from the text that they illustrate. The answer to possible criticism of the handsome format and quality of the paper used is, we understand, that pertinent preparations for the volume's publication had already been accomplished before the war time restrictions on printing paper, etc., had been put into effect. The obvious care and thought that have been put into this Centenary Volume have borne good fruit and a valuable chapter has been written into the history of American medicine. E. K.

PSYCHIATRY AND THE WAR. A Survey of the Significance of Psychiatry and Its Relation to Disturbances in Human Behavior to Help Provide for the Present War Effort and for Post War Needs. Edited by FRANK J. SLADEN, M.D., Physician-in-Chief, Henry Ford Hospital, Detroit Trustee, McGregor Fund. Contributions of the Conference on Psychiatry of the Univ. of Michigan and McGregor Fund. Pp. 505. Springfield, Ill.: Charles C Thomas, 1943. Price, $5.00.

IN this volume are gathered together some 30 papers and 2 symposia originally presented at the Ann Arbor Conference on Psychiatry held in October, 1942. Most of the best known names in American psychiatry may be found among the list of authors. Part 1 deals with the "Philosophy of Psychiatry," and comprises articles on the significance of psychiatry in sister disciplines such as pediatrics, geriatrics and internal medicine. Dr. Percival Bailey has contributed a particularly incisive paper on psychiatry and general surgery. Part 2 covers the topic "Research in Psychiatry." Part 3 is entitled "Psychiatry in the Training, Experience and Education of the Individual." Only

XUM

in Part 4, "Psychiatry and the War," do we find papers dealing with the psychiatric implications of the present world cataclysm.

One questions the propriety of the title given to a volume which devotes two-thirds of its text to matters not connected with war. One also questions the value of the book as a whole. Are short, 20-minute papers able to do justice to topics such as "Psychiatry and Family Life," "Psychiatry and Religion," "Psychiatry, Its Meaning and Scope"? This book is a collection of little papers on big subjects. Inevitably, the writers are somewhat overwhelmed by the topics selected for them. D. P.

MEDICAL EDUCATION IN THE UNITED STATES BEFORE THE CIVIL WAR. By WILLIAM FREDERICK NORWOOD, Associate Professor of the History of Medicine and Associate Dean in the School of Medicine, College of Evangelists, Los Angeles. Foreword by HENRY E. SIGERIST, Pp. 464. Philadelphia: Univ. of Penna. Press, 1944. Price, $6.00.

THIS carefully prepared, well documented, detailed, and unbiased study of American Medical Education during most of its preparatory period amply fulfills the Author's self imposed task of surveying "the rise and progress of the American system of medical instruction and the institutions of medical learning up to the time of the Civil War." Dr. Norwood's reasons for stopping at this point (closure of the Southern medical schools, the end of the critical period in the medical reform movement of the fifties, the Civil War's temporary stalemating of the movement to elevate medical education, and the bulkiness necessitated by inclusion of a longer period) are good and sufficient. Except for the lack of a sharp chronological end-point, however, it might more logically have been carried to the beginning of the renaissance in American Medical Education in the 70's; but this is by no means a vital consideration. Let us hope that a later volume—to which, for a while in these transition days, every succeeding year will be adding important material—will be forthcoming before too much time has elapsed and too much water has gone over the dam! E. K.

TECHNIQUE IN TRAUMA. Planned Timing in the Treatment of Wounds Including Burns. From The Montreal General Hospital and McGill Univ. By FRASER B. GURD, M.D., C.M., and F. DOUGLAS ACKMAN, M.D., C.M. In collaboration with JOHN W. GERRIE, M.D., C.M., EDWARD S. MILLS, M.D., C.M., JOSEPH E. PRITCHARD, M.D., FREDERICK SMITH, M.D. Preface by JOHN S. LOCKWOOD, M.D., Univ. of Penna., and Commentary by RALPH R. FITZGERALD, M.D., C.M., McGill Univ. Pp. 68; 17 figs.; 5 tables; 3 charts; 3 color charts; 3 color plates. Philadelphia: J. B. Lippincott, 1944. Price, $2.00.

THIS monograph contains 3 excellent articles reprinted from the *Annals of Surgery*, with additional text, with a commentary by Ralph R. Fitzgerald. The authors' practice and case reports are well set forth and are extremely interesting and valuable. Along with most other authors they have given up coagulation treatment of burns, and have laid down their step-by-step rules for the care of burns and wounds.

The work is a convenient form for reading, and if more widely adopted would help settle the "reprint problem" for both author and reader. J. B.

SYNOPSIS OF MATERIA MEDICA, TOXICOLOGY, AND PHARMACOLOGY. For Students and Practitioners of Medicine. By FORREST RAMON DAVISON, B.A., M.Sc., PH.D., M.B., Formerly Assistant Professor of Pharmacology in the School of Medicine, Univ. of Arkansas, Little Rock; Medical Department, The Upjohn Co., Kalamazoo, Mich. Third ed. Pp. 759; 40 illus. (4 in color); 35 tables. St. Louis: C. V. Mosby, 1944. Price, $6.50.

NEW editions of pharmacology texts can be evaluated best by comparison with the standard book in this field, Goodman and Gilman's "Pharmacological

Basis of Therapeutics;" such a comparison is decidedly unfavorable to Davison's 3rd edition. The latter suffers by the advocacy of many unsound procedures (such as the use of low chloride diet to eliminate bromide, the use of morphine in asthma, arsenic in malaria, atropine to arrest gastric and pancreatic secretions, 10% CO_2 inhalations for 5 to 10 minutes, etc.). In addition Davison often shows a poor understanding of physiologic mechanisms (see section on autonomic nervous system, renal function, anoxia). The diagrams are long outdated and often poorly chosen, the arrangement is not ideal ("miscellaneous drugs" include antimalarials, parenteral solutions, therapeutic gases, and sodium thiosulfate), the apothecaries system is often given preference over the metric, and there are numerous contradictions to confuse the student. This synopsis illustrates again the frequent association of inaccuracy with attempted condensation of a major medical science; nevertheless Davison's remains the best of the shorter books on Pharmacology.

J. C., Jr.

The 1943 Year Book of Pediatrics. Edited by Isaac A. Abt., D.Sc., M.D., Professor of Pediatrics, Northwestern Univ. Medical School; Attending Physician, Passavant Hospital; Consulting Physician, Children's Memorial Hospital and St. Luke's Hospital, Chicago. With the Collaboration of Arthur F. Abt, B.S., M.D., Associate Professor of Pediatrics, Northwestern Univ. Medical School; Associate Attending Pediatrician, Michael Reese Hospital; Attending Pediatrician, Chicago Maternity Center; Attending Physician, Spaulding School for Crippled Children and La Rabida Jackson Park Sanatorium, Chicago. Pp. 448; 76 figs. Chicago: Year Book Publishers, 1944. Price, $3.00.

The Year Book of Pediatrics is a collection of half-page or 2-page abstracts of the more important yearly contributions to pediatric literature. The several hundred articles reviewed have been selected with discrimination, and prepared with intelligent care. The abstractors have succeeded in conveying to the reader the meaty chief points of the original authors' presentations. Occasional notes inserted by the editor, and a large number of reproduced illustrations, add to the interest and value of the text. For the specialist this book is of value as a time-saving survey of annual progress; the general practitioner will find in it handy summaries of the latest views on nutrition, prophylaxis, diagnosis and treatment. The broad sweep of territory comprehended within the indefinite limits of pediatrics is emphasized by the fact that in a compilation such as this, only a small percentage of the articles quoted are from the familiar pediatric journals. The great majority have had to be picked from the great body of medical periodicals, native and foreign, which the average doctor never sees unless in the habit of browsing conscientiously through the reading room of a fine medical library. I. W.

Intracranial Arterial Aneurysms. By Walter E. Dandy, Adjunct Professor of Surgery in The Johns Hopkins Univ. Pp. 147; 55 figs.; 5 tables. Ithaca, N. Y.: Comstock Pub. Co., Cornell Univ., 1944. Price, $2.50.

Dr. Dandy presents in his latest monograph the results of probably the widest experience in the surgical attack of these formidable lesions. The general symptomatology, including the occasional occurrence of epilepsy and migraine, is discussed in detail. Consideration of the symptom-complexes caused by aneurysms arising from the various portions of the internal carotid artery and the Circle of Willis fails to establish clear localizing syndromes. Angiography was not generally employed and the consideration given this subject is meager. The potential value of the method is freely admitted, but Dr. Dandy has been fearful of the production of cerebral thrombi. It would seem that the wide experience of the many who have used thorotrast as the contrast media, without undue complications, would offset this fear.

A well-presented chapter on the embryology, anatomy and variations of

XUM

the Circle of Willis by D. H. Padget is included in this monograph. The relationship of the developmental anatomy of the Circle of Willis and the sites of the aneurysms found leads the authors to offer the well-conceived hypothesis that a congenital aneurysm occurs in connection with the incomplete involution of a temporary embryonic branch.

The surgical principles are clearly presented; the experiences detailed, some of them hair-raising, should be of immense help to those who would treat these lesions. Unfortunately, some confusion is caused by the failure to identify the cases considered in the text by other than their number in the series. This causes much turning back and forth from the unwieldly attached master tables in the back of the book for the reader to be fully oriented.

The illustrations, as is usual in Dr. Dandy's monographs, are excellent. The above-mentioned master tables, though difficult to handle, are of great value for detailed consideration of the case material. This monograph should serve well Dr. Dandy's purpose; that of stimulating the attack against these heretofore hopeless situations.

H. S.

ANATOMY AND PHYSIOLOGY. Laboratory Manual. By CATHERINE PARKER ANTHONY, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital, Cleveland, Ohio; Formerly Instructor of Anatomy and Physiology, St. Luke's Hospital, Cleveland, Ohio, and Assistant Instructor of Anatomy and Physiology, Frances Payne Bolton School of Nursing, Western Reserve Univ. Pp. 249; many illus. St. Louis: C. V. Mosby, 1944. Price, $2.00.

THIS manual offers basic material for a laboratory course in anatomy and physiology to preclinical nursing students, as a means of amplifying the textbook and lecture material.

The manual can be used for 30 to 70 laboratory hours. It follows closely the unit plan suggested in the Curriculum Guide for Schools of Nursing. Especially useful to instructors are suggestions for teaching hours and a list of equipment and material for each laboratory period.

This book may be used profitably in a school in which mimeographed laboratory sheets are not easily available and in which the laboratory work is not based on human or mammalian dissection by students. It may be correlated successfully with any standard textbook of anatomy and physiology for nurses.

H. F.

BACTERIAL INFECTION with Special Reference to Dental Practice. By J. L. T. APPLETON, B.S., D.D.S., Sc.D., Professor of Bacteriopathology and Dean, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, Univ. of Pennsylvania. Third ed., thoroughly revised. Pp. 498; 86 engravings; 5 plates. Philadelphia: Lea & Febiger, 1944. Price, $7.00.

THE author presents a thoroughly revised text on the host-parasite relationship with special reference to dental practice. The book was written for two purposes: (1) to give a comprehensive concept of infectious disease, and (2) to point out wherever a knowledge of infection will help the dentist in understanding or in solving his problems.

To carry out these purposes the book has been divided into 3 parts: Part I giving a minimum background on the morphology, physiology and ecology of the bacteria and filterable viruses; Part II treating the subject of infection in general; and Part III discussing the infections associated with the oral cavity and stressing the importance of dental health and infection in the general health of the patient.

In this 3rd edition, there has been increased emphasis placed on asepsis and surgical antisepsis. Part I has been increased to include material on the Pure Culture Study of Bacteria. Chapters have been added on the Ecology of Microörganisms of the Mouth, Actinomycosis and Osteomyelitis. The author stresses the importance of Oral Hygiene and places it as the ultimate goal of the text.

This text should have great value in the teaching of dentistry and in dental practice. First, to give the student the theories and fundamentals of infection and resistance to infection, and second, to give the practising dentist the practical points in understanding and solving his problems of asepsis and antisepsis as well as the rôle of the dental health in the general health of the patient.

F. E.

PHYSICAL FOUNDATIONS OF RADIOLOGY. By OTTO GLASSER, PH.D., Professor of Biophysics and Head of Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; EDITH H. QUIMBY, SC.D., Associate Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia Univ., New York; LAURISTON S. TAYLOR, PH.D., Chief of *X*-ray Section, National Bureau of Standards, Washington, D. C.; and J. L. WEATHERWAX, M.A., Philadelphia General Hospital and Graduate School of Medicine, Univ. of Pennsylvania, Philadelphia. Pp. 426; 95 figs.; 43 tables. New York and London: Paul B. Hoeber, 1944. Price, $5.00.

THE editorial team of this book leaves nothing to be desired. The editors are four authoritative physicists who have worked in the field of therapeutic radiology for many years. They have taught many students and know the weaknesses of physical education that is manifest in young doctors seeking training in radiology. In a small monograph of 426 pages, these authors have considered in a masterly way the various aspects of the physical problems of corpuscular and the electromagnetic wave radiation, the fundaments of electricity and magnetism, high voltage generators and Roentgen ray tubes, radioactivity—natural and artificial—the physical principles of Roentgen ray diagnostic features, the measurements of Roentgen ray and radium protection, and biologic reactions to radiation.

This book is prepared in such a way that it is easily understandable to one who has had a moderate amount of training in college physics. It supplies a real need in therapeutic and diagnostic physics.

Most of these authors have contributed many articles to the subjects discussed in this book, and it is from that background that they have provided an excellent small monograph. They have included an adequate number of diagrams and tables to explain most of the simple problems that confront the radiologist.

The publisher has provided good paper and most satisfactory printing. The Reviewer regards this book as an essential part of every radiologist's library.

E. P.

CÆSAREAN SECTION. The History and Development of the Operation From Earliest Times. By J. H. YOUNG, M.B., CH.B., D.T.M. and H. (EDIN.). Foreword by MILES H. PHILLIPS, M.D. (HON.), B.S., F.R.C.S., F.K.C.O.G. Pp. 254; 22 tables. London: H. K. Lewis, 1944. Price, 16s.

ANY exhaustive contribution to the history of medicine is very welcome, and especially one that deals with a procedure employed so universally as the delivery of the infant by the abdominal route. Young has made just such a contribution in his volume dealing with cæsarean (or as we Americans are accustomed to spell the word, cesarean) section. This book not only supplies a remarkably full history of this classical operation but also stresses the development of the various modifications of the operation. Many interesting cases are cited, including mention of the first operation performed in the United States (1822). The patient, a 14 year old quadroon, illegitimately pregnant with twins, opened her own abdomen with a razor while lying on a snowbank. Her first infant was born *per vias naturales*, and its twin through the abdominal wall. The patient survived her operation, and was known to be living 6 years later.

The volume is fully documented and contains a complete bibliographic index. Although the extraperitoneal operation is considered, the omission of the Waters technic, developed in this country, no doubt resulted from the

XUM

fact that it is a very recent development. The Reviewer recommends this important volume to all obstetricians, and to every one interested in the history of surgery.

D. M.

HYDRONEPHROSIS AND PYELITIS (Polynephritis) OF PREGNANCY. Etiology and Pathogenesis. An Historical Review. By H. E. ROBERTSON, M.D. Philadelphia: W. B. Saunders, 1944. Price, $4.50.

Too often the practitioner of medicine is conversant only with the dominant contemporary theories of disease, and is wholly ignorant of their origins. This scholarly review of the development of our concepts of hydronephrosis and pyelitis in pregnancy is proof that American medicine has reached the stage where it may pause now and then to evaluate contemporary opinion in the light of previous experience. How thoroughly the author has done this for his chosen subject is indicated by the length of the bibliography which numbers almost 1000 entries. Unique is a chapter devoted to a review of textbooks and their method of dealing with the problem. For the textbook, even more than the original article, moulds the pattern of thought in each new generation of physicians. It is hoped that this monograph will be only the first of many dealing with the "Entwicklungsmechanik" of modern medicine.

H. S.

AUTONOMIC REGULATIONS. By ERNST GELLHORN, M.D., PH.D., Professor of Physiology, College of Medicine, Univ. of Illinois. Pp. 373; 80 illus. New York: Interscience Publishers, Inc., 1943.

THIS book is a compounding of some 55 original papers published by the author during the years 1939–1942, along with a review of the literature. Some of the material represents unpublished observations of the author, much of it unconfirmed and not infrequently comprising evidence apparently obtained from a single animal experiment. The book is highly repetitious, and one has the feeling that the subject matter might have been presented better, with less confusion, in considerably less space. Nevertheless, it contains interesting data which should be unusually stimulating to investigators.

J. C.

MANUAL OF HUMAN PROTOZOA. By RICHARD R. KUDO, D.Sc., Associate Professor of Zoölogy, The University of Illinois. Pp. 125; 29 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $2.00.

THIS little book contains all the information necessary for efficient examination of blood, tissues and excretions to determine whether or not protozoan parasites are present. Descriptions are complete, drawings accurate—although they do not allow for variations—and directions are clearly worded. It will be especially valuable to technicians in clinical laboratories.

H. R.

MANUAL OF THE DISEASES OF THE EYE. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York; Formerly Chief of Clinic and Instructor in Ophthalmology, Medical Department of Columbia Univ.; and Director of the Eye Service at Bellevue Hospital, New York. With the assistance of CHARLES A. PERERA, M.D., Associate in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia Univ., New York; Assistant Attending Ophthalmologist, Presbyterian Hospital, New York. Eighteenth ed. Pp. 520; 387 figs. (32 plates, 93 colored figs.). Baltimore: William Wood., 1943. Price, $4.00.

THIS new edition retains the excellence of previous ones as a textbook for students and general practitioners. There are many minor changes and corrections. The sections on therapy of the various ocular infections now include

the use of penicillin, as well as the more recent sulfa drugs. The sections on compensation for eye injuries and the ocular requirements for admission to the various armed services have been brought up to date. F. A.

PRACTICAL MALARIAL CONTROL: A HANDBOOK FOR FIELD WORKERS. By CARL E. M. GUNTHER, M.D., B.S., D.T.M. (SIDNEY), Field Medical Officer, Bulolo Gold Dredging Limited, Territory of New Guinea, at present with the Australian Medical Corps. Foreword by PROF. HARVEY SUTTON, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R.SAN.I. Pp. 91. New York: Philosophical Library, 1944. Price, $2.50.

THIS practical handbook is concerned with the problem of control, diagnosis and treatment of malaria. The experience of the author is extensive and it should prove to be a valuable guide to those combating malaria in the field. However, his recommendations on the drug prophylaxis and treatment of malaria do not agree with the current concepts originating from the Offices of the U.S.A. Surgeons-General. The use of thick films in the diagnosis of malaria should be more fully dealt with, as it is now a recognized practical field method. The discussion of mosquito control methods is excellent and would alone be sufficient to recommend the book. R. J.

NEW BOOKS

Urological Surgery. By AUSTIN INGRAM DODSON, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia; Urologist to the Hospital Division, Medical College of Virginia; Urologist to Crippled Children's Hospital; Urologist to St. Elizabeth's Hospital; Urologist to St. Luke's Hospital and McGuire Clinic. With contributions by 7 well-known authorities. Pp. 768; 576 illus. St. Louis, C. V. Mosby, 1944. Price, $10.00.

Fertility in Women. By SAMUEL L. SIEGLER, M.D., F.A.C.S., Attending Obstetrician and Gynecologist, Brooklyn Women's Hospital; Attending Gynecologist, Unity Hospital; Assistant Obstetrician and Gynecologist, Greenpoint Hospital; Attending Sterility Clinic, Greenpoint Hospital; Consultant in Gynecology, Rockaway Beach Hospital; Diplomate, American Board of Obstetrics and Gynecology; Fellow, New York Academy of Medicine; Member, Society for the Study of Internal Secretions. Foreword by ROBERT LATOU DICKINSON, M.D. Pp. 450; 194 illus. Philadelphia, J. B. Lippincott, 1944. Companion book to Fertility in Men. In slip case, $8.00.

Fertility in Men. By ROBERT SHERMAN HOTCHKISS, B.S., M.D., LT. COMM. (M.C.), U.S.N.R. (on active service), Assistant Professor of Urology, New York Univ. Medical College; Instructor in Surgery (Urology), Cornell Medical College; Assistant Visiting Attending Physician, Department of Urology, Bellevue Hospital; Assistant Visiting Attending Physician in Surgery (Urology), New York Hospital; Chief of Urological Clinic, New York Univ. Medical College Clinic. Foreword by NICHOLSON J. EASTMAN, M.D. Pp. 216; 95 illus. Philadelphia: J. B. Lippincott, 1944. Companion book to Fertility in Women. In slip case, $8.00.

Hypertension and Hypertensive Disease. By WILLIAM GOLDRING, M.D., and HERBERT CHASIS, M.D. Dedication to HOMER W. SMITH. Pp. 253; 53 figs. New York: The Commonwealth Fund, 1944. Price, $3.50.

Rebel Without a Cause. The Hypoanalysis of a Criminal Psychopath. By ROBERT M. LINDNER, PH.D., U. S. Public Health Service (R), Psychologist; U. S. Penitentiary, Lewisburg, Pa.; Lecturer in Criminology, Bucknell Univ. Introduction by SHELDON GLUECK, LL.B., PH.D., and ELEANOR T. GLUECK, ED.D. Pp. 295. New York: Grune & Stratton, 1944. Price, $4.00.

XUM

Technic of Electrotherapy and Its Physical and Physiological Basis. By STAFFORD L. OSBORNE, M.S., PH.D., Assistant Professor, Department of Physical Therapy, Northwestern Univ. Medical School; and HAROLD J. HOLMQUEST, B.S., B.S.(M.E.), Lecturer in Applied Physics, Dept. of Physical Therapy, Northwestern Univ. Medical School. Pp. 780; 240 figs., having 293 illus.; 72 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, $7.50.

Medical Education in the United States Before the Civil War. By WILLIAM FREDERICK NORWOOD, Associate Professor of the History of Medicine and Associate Dean in the School of Medicine, College of Evangelists, Los Angeles. Foreword by HENRY E. SIGERIST. Pp. 464. Philadelphia: Univ. of Pennsylvania Press, 1944. Price, $6.00.

Organic Chemistry. By LOUIS F. FIESER, Sheldon Emery Professor of Organic Chemistry, Harvard Univ.; and MARY FIESER, Research Chemist. Pp. 1112; numerous illustrations. Boston, Mass.: D. C. Heath, 1944. Price, Trade Edition, $8.00; College Edition, $6.00.

The Romance of Medicine. The Story of the Evolution of Medicine From Occult Practices and Primitive Times. By BENJAMIN LEE GORDON, M.D., Member, American Association of the History of Medicine; Attending Ophthalmologist to the Shore Memorial Hospital, Somers Point, N. J., and to Atlantic County Hospital for Tuberculosis, Northfield, N. J. Authorized Medical Examiner for Civil Aeronautics Administration, Dept. of Commerce, Washington, D. C. Formerly Associate Ophthalmic Surgeon of St. Agnes Hospital, Philadelphia. Pp. 624; 147 illus. Philadelphia: F. A. Davis, 1944. Price, $5.00.

NEW EDITIONS

The Youngest of the Family. A Manual for the Inexperienced Mother. By JOSEPH GARLAND, M.D., Physician to Children's Medical Dept., Massachusetts General Hospital; Consulting Pediatrician, Massachusetts Eye and Ear Infirmary; Instructor in Pediatrics, Harvard Medical School. Revised ed. Pp. 182. Cambridge, Mass.: Harvard Univ. Press, 1943. Price, $2.00.

Quick Reference Book for Medicine and Surgery. A Clinical, Diagnostic, and Therapeutic Digest of General Medicine, Surgery, and the Specialties. By GEORGE E. REHBERGER, A.B., M.D. Twelfth ed. Pp. 1460. Philadelphia, London, Montreal: J. B. Lippincott, 1944. Price, $15.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author is the manuscript is accepted.

For the balance of the war, 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.